Organic Chemistry

A GUIDED INQUIRY

SECOND EDITION

Andrei Straumanis

POGIL

Organic Chemistry
A Guided Inquiry
Second Edition

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a process oriented guided inquiry learning course

Andrei Straumanis

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The first edition was dedicated to our then infant son, Milo. We now have another son, Luca.

This second edition is dedicated to them, collectively, and to teachers (and parents) everywhere doing their best to facilitate quality group work.

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Acknowledgements

In preparing a ChemActivity for publication, nothing substitutes for watching real students work in a real class setting. My students taught me so many valuable lessons that have been folded into this second edition. Thanks!

Thanks to my colleagues at the College of Charleston for going out of their way to support my use and development of POGIL. Special thanks to Rick Heldrich, Marion Doig, Justin Wyatt, Charles Beam, and Gary Asleson, the departments' other organic chemistry teachers, for teaching me a lot about chemistry and chemistry students. I would also like to extend my gratitude to department chair, Jim Deavor, and Science and Mathematics Dean, Norine Noonan, for supporting me on this endeavor.

Many of the over 100 faculty who used the first edition have contributed to improvements in the second edition. Thanks for all of your suggestions and corrections. Special thanks to Tom Eberlein of Penn State Harrisburg for applying his deep knowledge of organic chemistry, his incredible attention span, and his rich understanding of POGIL to his reading of this second edition.

Thanks to the POGIL Project and to its growing number of participants. My mentor and friend Rick Moog, of Franklin & Marshall College, deserves special thanks. Rick's contagious enthusiasm for guided inquiry inspired me and many others to embark on this path.

Funding for the Large Class POGIL Project, of which this workbook is a key part, was provided by the United States Department of Education's FIPSE Fund under grant number P116B060026. Thanks to my collaborator on this project, Suzanne Ruder of Virginia Commonwealth University.

General support for the POGIL Project is provided by NSF CCLI Grants DUE-0231120, 0618746, 0618758, and 618800.

Finally, thanks to my family, who has suffered through way too many hours of daddy being glued to his computer making "chemistry drawings."

Comments from Faculty about this Book

'Organic Chemistry: A Guided Inquiry' was a true revelation to me. In adopting a POGIL format in a large classroom my day-to-day preparations were comparable in intensity and duration to the time I spent preparing for traditional lectures. In my years as a college educator, I have not seen anything as pedagogically powerful as a POGIL class using Straumanis' workbook. I believe the future of college 'teaching' lies in this type of 'learning.' I give Straumanis my highest rating.

Dr. Stefan Kraft, Kansas State University

This workbook has revolutionized the way I teach organic chemistry. The students process the material in logical steps, are active learners in the classroom, and the end result is a deeper understanding of organic compounds and reactions. I highly recommend this book!

Dr. Bruce J. Heyen, Tabor College

The guided inquiry helps me [the professor] think more like a student and it helps me cover material more efficiently.

Dr. Dan Esterline, Heidelberg College

Organic Chemistry: A Guided Inquiry is a great way to teach and learn organic chemistry. The students love the interactive nature of class time. I become better acquainted with each of my students, which enables me to tailor my teaching to maximize each student's learning. It has transformed the way I teach.

Dr. Timothy M. Dore, University of Georgia

It is fabulous to see the increase in understanding of reaction mechanisms. The students learn the mechanisms by working together, discussing, and sometimes arguing about them, but they don't memorize them. What I really like about the approach is that when class is ending, the students are still working. There is no clock watching!

Dr. William Wallace, Barton College

I am thankful that I decided to use the Guided Inquiry approach in my class. Students have responded in a very positive manner. Other faculty, too, see a change in the students' attitude towards learning Organic Chemistry.

Dr. Karen Glover, Clarke College

I have been using the Guided Inquiry Organic Chemistry materials since they were in manuscript form, and I am delighted about the second edition. The ChemActivities do an excellent job enabling students to build on their knowledge to develop new knowledge and to apply chemical concepts to new situations. Students enjoy organic chemistry and they learn it well because they engage directly with the material and with their peers.

Dr. Laura Parmentier, Department Chair, Beloit College

Watching my students engaged in discussing organic chemistry in their groups during organic class has convinced me that I made the right decision to change to POGIL after twenty years of brilliant lecturing. Straumanis' ChemActivities really do help the students learn organic much better than my lectures ever did.

Dr. Barbara Murray, University of Redlands

To the Instructor

These materials are flexible. The first edition was used in organic courses at over 100 different colleges and universities to support student active learning in a wide variety of classroom settings ranging from four to four hundred students. The following attributes are common to many of these classrooms:

- During class, students work in teams of 3 or 4 to solve the Critical Thinking Questions, which are carefully designed to guide students toward discovering a chemical concept.
- There is only occasional lecturing. Usually lectures are less than five minutes, and not used to cover new material, but rather to reinforce or expand on topics already explored during group work.
- The instructor serves as the facilitator of learning, observing student group work, asking questions, leading discussions, and answering student questions[1] in a way that helps groups *discover* concepts.

The classroom environment described above and the teaching method associated with it are called Process Oriented Guided Inquiry Learning (POGIL). The POGIL Project estimates that in Fall 2007 over 20,000 college chemistry students experienced POGIL in their classroom.

If you are having trouble picturing how you could do this in your classroom (especially a lecture hall of hundreds of students), come visit my classroom, or attend a free NSF/US Department of Education-FIPSE sponsored workshop and get your questions answered. POGIL materials are available for an ever expanding array of chemistry sub-disciplines. Full details can be found at www.POGIL.org.

Another good resource is the instructor-only yahoo group moderated by the author of these materials, and dedicated to POGIL Organic Chemistry (find it by searching "**GIorganic**" at groups.yahoo.com).

Forward on Process Oriented Guided Inquiry Learning (POGIL)

by Rick Moog, Jim Spencer and John Farrell, authors of *Chemistry: A Guided Inquiry* (for General Chemistry) and two volumes of *Physical Chemistry: A Guided Inquiry*.

These guided activities were written because much research has shown that more learning takes place when the student is actively engaged and when ideas and concepts are developed by the student, rather than being presented by an *authority*—a textbook or an instructor.[2] The *ChemActivities* presented here are structured so that information is presented to the reader in some form (an equation, a table, figures, written prose, etc.) followed by a series of Critical Thinking Questions that lead the student to the development of a particular concept or idea. Learning follows the scientific process as much as possible throughout. Students are often asked to make predictions based on the model that has been developed up to that point, and then further data or information is provided that can be compared to the prediction. In this way, students simultaneously learn course content and key process skills that constitute scientific thought and exploration.[3,4,5]

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[1] A note on the question: *Is our answer right?* **It can be problematic to answer *or refuse to answer* this question.** Alternatively, ask students to explain *why* they think their answer is right or wrong, or remind them to go through the steps listed in the **IntroActivity** under "What can we do if our group is uncertain…"

[2] Johnson, D. W.; Johnson, R. T. *Cooperative Learning and Achievement.* In Sharon, S. (Ed.), *Cooperative Learning: Theory and Research*, pp 23-37, New York: Praeger.

[3] *How People Learn: Brain, Mind, Experience, and School*; Bransford, J.D., Brown, A.L., Cocking, R.R., editors; National Research Council, National Academy Press, Washington, D.C. 1999.

[4] Farrell, J.J., Moog, R.S., Spencer, J.N., "A Guided Inquiry General Chemistry Course." *J. Chem. Educ.*, 1999. 76: 570-574.

[5] Spencer, J. N. "New Directions in Teaching Chemistry." *J. Chem. Educ.* 1999, *76*, 566.

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Notes on the Second Edition

Overview: This edition contains sixty-six 45-minute ChemActivities covering the major topics of a two-semester organic course. In this edition, the topics are delivered in a sequence that closely follows that of most traditional texts, making it possible to use this book in conjunction with any textbook.

An *IntroActivity* has been added which uses guided inquiry techniques to teach students key strategies for making the most of these materials.

This workbook contains the consensus topics that most every organic chemistry course covers. Activities on additional topics will be added to the POGIL website at www.pogil.org/straumanis as they are tested and refined. Users of this workbook have posted some of their own activities on the *Yahoo* discussion group for Guided Inquiry Organic Chemistry. You can join this instructor-only group by going to groups.yahoo.com and searching for **GIorganic**.

To help students find and correct their own mistakes the author has added *Check Your Work* sections throughout the workbook that provide, not answers, but extra information that help students self-assess and self-correct as they will need to do in the real world (where there is no answer key).

Synthetic Transformations needed for organic synthesis are now boxed and labeled within each activity *and* listed at the end of the book with a reference to the section where each was first introduced.

Clearly marked *Memorization Tasks*, have been added, not to encourage more memorization (since many organic chemistry students already rely inappropriately on memorization), but rather to help students realize that everything outside of the *Memorization Task* boxes is derived from the key concepts reinforced throughout the book and therefore should not be memorized, but *understood*.

To facilitate *useful* limited memorization, the author has provided a novel strategy for making and effectively using note cards to memorize reactions in a group setting.

Improved, student-friendly algorithms for determining *cis/trans*, *E/Z*, R/S, and other parameters help prevent students from getting hung up on these common sticking points.

The second edition expands on a rigorous, useful, and unique method of explaining and using pK_a to solve a wide range of acid-base and non-acid/base problems.

Special ChemActivities called *Synthesis Workshops* are devoted to helping students understand the arts of *Synthesis and Retro-synthesis*, and are reinforced by a dramatically expanded array of synthesis practice problems placed throughout the book.

A unique *Flow Chart Decision Tree for Substitution and Elimination* has been added to help students develop a big-picture understanding of this complex topic. It is not designed to be memorized; instead, the accompanying ChemActivity guides students to understand the reasoning behind each branch point on the decision tree.

Spectroscopy Activities have been added and expanded. These lab activities can be inserted anywhere, used as take-home exercises to prepare students for lab, or used in place of laboratory lectures.

Improved and expanded *Nomenclature Worksheets* walk students through the IUPAC rules for naming key functional groups. These four activities can be used in class or assigned as homework, and are placed in the text so that students learn rules for naming each functional group in proximity to the activity in which the functional group is introduced.

Each chapter ends with two sections, *The Big Picture* and *Common Points of Confusion*. The content of these sections is similar to what you might find in a Chapter summary in a traditional textbook, but the way it is delivered is special. Traditional textbook summaries lay out concepts in clear and economical language, but the special summaries found in this book go on to help students fit these new ideas into their current understanding. *The Big Picture* and *Common Points of Confusion* sections are based on thousands of hours of POGIL classroom experience spent listening to student groups discuss and conceptualize the material. At the root of the POGIL method is the assertion that effective teaching is much more than clear delivery of information (output from the expert), and that the hardest part of the process, the part where learning typically bogs down, is in the input phase, *the conceptualization of the material by the student*. It is for this reason that the special chapter summaries found in this workbook deliver content *along with guidance on how students might make sense of key concepts*, including commentary on where and why students typically get lost, confused or frustrated.

Instructor materials are available online as free password-protected downloads on the Instructor Website, accessible via college.hmco.com/pic/straumanis2e.

Comments from Students about this Workbook

I didn't get tired during class because I was constantly thinking and working instead of in a lecture class where I just listen and get easily tired.

The act of explaining the concept forced me to clarify the concept in my own head.

Class time was actually learning time, not just directly-from-ear-to-paper-and-bypass-brain-writing-down time. Learning the material over the whole term is far easier than not "really" learning it until studying for the tests.

I wasn't just blindly copying notes on the board but actually working through problems and learning.

Overall, I was far less stressed than many of my friends who took the lecture class. They basically struggled through everything on their own.

Group work has helped me find motivation for studying.

It was hugely beneficial to be able to discuss through ideas as we were learning them; this way it was easy to immediately identify problem areas and work them out before going on.

The method of having us work through the material for ourselves— as opposed to being told the information and trying to absorb it—makes it seem natural or intuitive. This makes it very nice for learning new material because then we can reason it out from what we already know.

I felt like I was actually learning the information as I received it, not just filing it for later use. The format helped me retain much more material than I have ever been able to in a lecture class, and the small, group atmosphere allowed me to feel much more comfortable asking questions of both other students and the professor.

Through working in groups it was nice to see where everyone else was in understanding the material (i.e. to know where other people were having trouble too).

We were able to discover how things happened and why for ourselves…instead of being told.

Advice from Students to Students

Don't let yourself take the course lightly just because class is fun and relaxed (and goes by fast!). Do the homework and reading.

Give yourself some time to settle into group learning. Lots of us did not think we would like it or that it would work. It does.

Don't fall behind. Playing catch up is not fun. Don't be afraid to ask questions and argue in your group. That is the way learning is done in this class.

You may think (like I did) that group work in organic chemistry is a bad idea. (I thought it would be the blind leading the blind.) But it really does work. I experienced both. I had lecture for Organic 1, and I have really enjoyed the group work in Organic 2.

Find a study group ASAP and meet regularly every week. I wish I had done this sooner.

To the Student

To be successful in most any organic chemistry course you must…

1. Put in the time—2 to 5 hours of work outside class for each hour in class
2. Utilize a wide range of resources including molecular models, your textbook, your instructor, homework, TA's, online resources, etc.
3. Find someone with whom to study (a study partner or study group)

Some version of this advice is routinely given to students and is found in many organic chemistry syllabi and textbooks. Students often begin their course with the intention of following this very sound advice, but find that such advice is easy to give *but hard to follow*.

This workbook and the teaching method associated with it (called POGIL) are designed to help.

Why does POGIL work?

There are many reasons. (**A sampling of student comments and advice are on the previous page.**)

- The simplest reason might be that POGIL students never fall asleep in class. You may be amazed at how short 50, 75, or even 120 minutes of organic chemistry class can feel.
- Instead of copying notes from the board, you spend most of class time learning. Time goes by fast because POGIL gets you **actively engaged** and thinking in class.
- Much of a POGIL class is spent working in groups. This helps you learn how to function effectively as part of a group, and helps you find a **compatible study partner** for outside of class.
- A student who is engaged and networked with at least one other student will study more, use appropriate resources more effectively, get a better grade, and **have more fun**.

What should I do if I'm uncertain about POGIL?

You are not alone. Few students are sure about POGIL at the start, especially those who have been very successful in their lecture-based science courses. The best thing to do is to **suspend your doubts and work hard on the organic chemistry for a week or two until you get a feel for how POGIL works**.

Don't get off to a bad start by spending lots of energy fighting against your instructor's choice to use POGIL. For now, give your instructor and this workbook the benefit of the doubt. Chances are you will like it once you get used to it. By the end of a POGIL course few students (only 7% on average) still say they prefer lecture over POGIL.

If you have questions or concerns about POGIL, use email or office hours to bring them up. Your instructor is using POGIL because (s)he cares deeply about teaching and learning, and will listen with interest to your concerns; however, it is best to refrain from openly negative comments during class.

Finally, if you find an error, have a comment, or a suggested improvement for the author of this book, please email Andrei@pogil.org.

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IntroActivity: Organic Chemistry: *A Guided Inquiry*

Model 1: What is Organic Chemistry?

- A partial periodic table is shown below. (There is a full **periodic table** at the back of this book.)
- This course will focus on the shaded elements: those commonly found in organic molecules.
- The number above each column indicates the **number of covalent bonds that an element in that column will typically make**. (The first element in each column is shown as an example.)

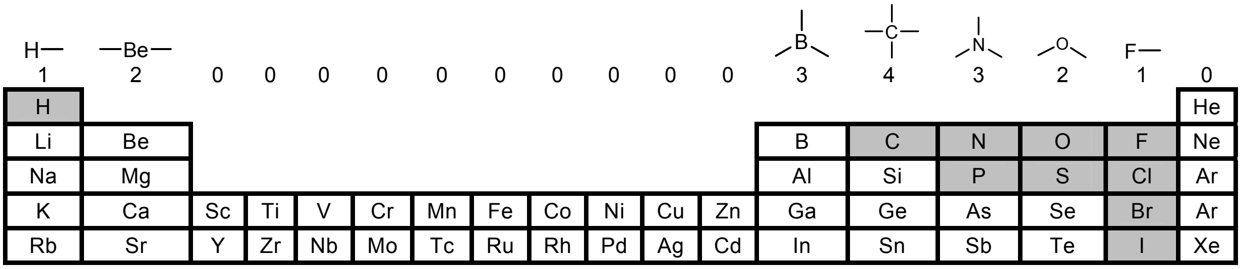

H— —Be— B C N O F—
1 2 0 0 0 0 0 0 0 0 0 0 3 4 3 2 1 0
H He
Li Be B C N O F Ne
Na Mg Al Si P S Cl Ar
K Ca Sc Ti V Cr Mn Fe Co Ni Cu Zn Ga Ge As Se Br Ar
Rb Sr Y Zr Nb Mo Tc Ru Rh Pd Ag Cd In Sn Sb Te I Xe

Figure A: Partial periodic table

Work together with your group to answer the following Critical Thinking Questions (CTQ's).

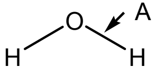
Critical Thinking Questions

1. (**E = "Exploration Question"**) List a few elements you expect to find in organic molecules.

2. (E) Where in this book can you find a full periodic table?

3. (E) How many bonds does a carbon atom typically make?

4. (E) In the drawing of water (H_2O) below are O and H making their typical number of bonds?



A bond is drawn as a line between atom letters.

5. Draw a molecule composed of only C and H with exactly one C atom and some number of H atoms in which both C and H are making their typical number of bonds.

Model 2: Frequently Asked Questions about Using this Workbook

How do I use this workbook during class?

I. **READ** the section labeled **MODEL** (*e.g.,* Model 1 on the previous page).

II. **READ** the **CRITICAL THINKING QUESTION(S)** (CTQs) following the model.

III. **COMPARE** your answer to your groupmates' answers.

IV. **DISCUSS & RESOLVE** any differences, and move on to the next question.

What can we do if our group is uncertain of an answer to a CTQ during class?

- Have one person in the group **READ THE QUESTION OUT LOUD.**
- **READ THE *NEXT* QUESTION** or Model (this can help confirm your answer).
- Check the answers of a nearby group (refrain from hunting through the textbook during class).
- Manager ask instructor a question that gets at the heart of your confusion. *(If you simply ask **"Is our answer correct?"** instead of a Yes or No, your instructor may ask you to explain why you are unhappy with your answer.)*

What are some strategies for improving in class group work?

- **Don't blurt out your answer** (even if you are certain you are correct). Instead, **ASK** a groupmate what he or she thinks the answer is.
- Look for questions marked **(E) for "Exploration." These are designed to be quick and easy.** The answer to an (E) Question can usually be pulled directly from the Model.
- Decide on a **Group Manager** each day. One job can be to ask: "Is everyone ready to move on?"
- If you feel rushed or behind your group during class, **read the ChemActivity before class** and jot down possible answers to the first few Critical Thinking Questions (in pencil) in the margins.
- **Do a self-assessment**. Each person writes down a strength of the group and an area for improvement. Then discuss the results. (Or find yourself on the table and the end of this activity.)

Does "group work" mean "*group grading*"?

No. Your grade will depend on ***your scores on quizzes and exams***, ***taken individually***, and reflect your *personal* understanding of the material. Research on learning shows group work enhances this understanding and boosts scores on exams, so take group work seriously, even if it is not graded.

Critical Thinking Questions

6. (E) What does the letter "E" at the start of this question (and CTQ's 1-4) stand for?

7. Speculate as to the purpose of CTQ's marked with an (E).

8. Most activities in this book start with "E" questions designed to make you look carefully at ("Explore") the most important parts of the Model, and begin to see the patterns and underlying concepts. Is this information consistent with your answer to the previous question?

9. (E) According to Model 2, what are the first two things your group should do if you are not sure of an answer to a Critical Thinking Question?

10. What is the purpose of CTQ 8 in relation to CTQ 7?

11. If one person consistently blurts out the answer to each question, how might this impact the learning of the other members of the group?

12. (E) What is something you can do before class if you feel you are always one step behind the rest of your group during in-class group work?

13. Why should you take group work seriously even if it is not graded?

FOR THIS PAGE YOU WILL BE PASSING YOUR WORKSHEETS AS YOU DO THE ACTIVITY.

- **After you complete CTQ 14 on your own worksheet, pass it to a groupmate. (Pass to the right if you are in a circle.)**
- **Now answer CTQ 15a on this new worksheet and pass again.**
- **Keep doing this through CTQ 16; then get your own worksheet back.**

Model 3: Why Carbon?

Table A: X—Y Bond Strengths (Average Bond Dissociation Energies in kcal/mole)

	H	C	N	O	Si	P	S	F	Cl	Br	I
H	104	99	93	111	70	77	81	135	103	88	71
C	99	83	73	86	83	73	65	116	81	68	51
N	93	73	38	55	*	*	*	*	*	*	*
O	111	86	55	35	110	96	87	*	*	*	*
Si	70	83	*	110	52	*	*	132	86	*	*
P	77	73	*	96	*	51	*	*	79	65	*
S	81	65	*	87	*	*	54	*	*	*	*
F	135	116	*	*	132	*	*	36	*	*	*
Cl	103	81	*	*	86	79	*	*	58	*	*
Br	88	68	*	*	*	65	*	*	*	46	*
I	71	51	*	*	*	*	*	*	*	*	36

* Less common or uncommon bond

Critical Thinking Questions

14. (E) What is the bond strength of a C—F bond (in kcal/mole)?

15. The grey boxes in Table A give bond strengths for homo-atomic bonds (e.g., H—H, C—C, etc.). Note that "homo" = same.

    a. (E) Which two atoms stand out as making the two strongest homo-atomic bonds?

    b. (E) Which two atoms commonly make bonds with all other atoms listed?

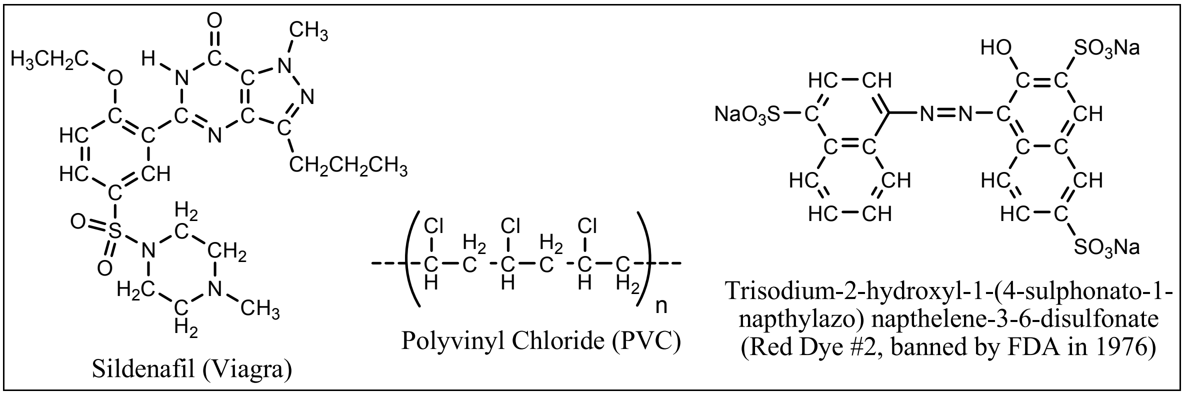
    c. Which one atom is likely to form the backbones of stable chains, branching chains, and rings with a wide variety of other atoms attached to these backbones? Explain your reasoning.

16. Are your answers above consistent with the fact that C and H are found in 99% of all known molecules? (A molecule is almost always considered an **organic molecule** if it contains C and H.)

17. Did passing your worksheets affect your confidence in your answers? If so, how?

18. In what ways did passing your worksheets change the way your group was interacting with each other?

Model 4: Why study organic chemistry?



Sildenafil (Viagra)

Polyvinyl Chloride (PVC)

Trisodium-2-hydroxyl-1-(4-sulphonato-1-napthylazo) napthelene-3-6-disulfonate (Red Dye #2, banned by FDA in 1976)

Figure B: Sampling of products synthesized by organic chemists.

Humans continue to invest great energy in the study of organic chemistry largely because the end products can be incredibly useful (e.g., PVC, above). To facilitate the production of new and even better drugs, materials, dyes, food additives, etc., organic chemists use special tools to observe what happens when two (especially new) chemicals are mixed. The set of theories and rules you will learn in this course are the result of such observations made by organic chemists mostly over the past 100 years.

By the end of the last century, biochemistry began to take center stage in many academic and commercial arenas. Though this course focuses on simple, non-biological molecules, you will find that learning the basics of organic chemistry greatly enhances your ability to understand biochemistry.

Perhaps the best reason to study organic chemistry is that its richness and complexity make it a perfect playing field for honing your analytical and problem-solving skills. These skills (along with communication and teamwork skills) are what employers and graduate school admissions committees are looking for in an applicant. Success in this environment shows that you can solve problems in *their* rich and complex environment, be it medicine, research, business, or any other field.

Critical Thinking Question

19. Why do admissions committees and employers care how you do in organic chemistry even if you are not applying for a position that requires knowledge of organic chemistry or biochemistry?

Model 5: Exercises (and other Homework)

In future ChemActivities, when you get to the heading "**Exercises**" you have completed the in-class portion of the ChemActivity. If your group finishes early, begin working on these Exercise questions.

What should I do for homework after each class?

- Complete any unfinished parts of the ChemActivity. (It is best if you can get together with your group after class. Now is a good time to exchange phone numbers or agree on a meeting place.)
- Attempt all homework problems without peeking at the answers. As a last step **read the assigned sections of the textbook** to check your understanding of the ChemActivity *you just completed.*

If the homework and reading do not make sense, then you did not get all you were supposed to from the in-class activity, and YOU WILL NOT DO WELL ON THE UPCOMING QUIZ or EXAM.

Go back through the activity or seek help from a student or instructor until you can do the homework.

Do not put this off and let yourself fall behind. Each topic builds on the next like a pyramid. The horror stories you hear about organic chemistry likely come from students who fell behind and tried to pile new topics onto an incomplete and shaky foundation.

Invest now in a solid foundation: Finish each activity. Do all your homework. Keep a list of questions, and track down the answers before the next class. This usually takes 2-5 hours for each class.

Critical Thinking Questions

20. According to Model 5, is the reading assigned in the Exercises of this activity designed to reinforce topics you worked on today in class, or introduce new topics you will encounter next class?

21. In guided inquiry learning, students construct their own answers to CTQ's (there is no key), and so some students therefore worry that their group's answers are wrong or that they are missing key concepts. How can you tell if you have a misconception or a hole in your understanding?

22. What are two things you should do if you suspect you have a misconception or you do not understand something that seems important?

23. Take a few minutes to jot down at least one item in each of the following categories.
    a. **strength** of your group, and how this strength helped you learn

    b. **area for improvement**, and a change your group could make to improve in this area

    c. **insight** you had today about teaching or learning

24. Share your answers to the previous question with your group mates. Start with each person stating a strength of the group—then go around again and share an area for improvement. If time permits you may share your insights. Use the space below to jot down items you want to share if the instructor calls for a group spokesperson to report a strength, improvement, or insight.

Exercises

1. For each row on the table below, circle the statement that best describes **YOU** in terms of participation in your group during the recently completed class. (Not to be collected by the instructor.)

Excellent (4)	**Good (3)**	**Fair (2)**	**Poor (1)**
Lead *and* share the lead without dominating	Lead but dominate a bit	Follow but never lead	Actively resist group goals
Actively pace group so everyone is on the same question & finish on time	Aware of time issues but don't actively work to keep group together & on pace	Don' t think much about group progress or timing	waste lots of group time, fall behind, or work ahead
Stay on task and keep others on task	Keep self on task	Sometimes get group off task	Often get group off task
Actively create environment where everyone feels comfortable participating	Try to engage others in a helpful and friendly way	Rarely initiate interactions, but respond in a friendly way when others initiate	Observe silently, and offer little when others try to engage you
Express disagreement directly and constructively	Usually express disagreement directly	Avoid confrontation even when angry or frustrated	Let negative emotions get in the way of team goals
Enthusiastic and positive	Moderately enthusiastic	Show little enthusiasm	Negative or unenthusiastic
Always come prepared	Usually prepared	Occasionally unprepared	Usually unprepared

Figure C: Self-Assessment of *your* participation in your group

2. Calculate a "participation score." Give yourself 1 point for an item in the Poor column, 2 points for an item in the Fair column, etc., and add up all your points.

3. (Optional) Share this **self-assessment** with your group mates (e.g., at the start of next class).

4. Check your course syllabus for assigned reading or problems. There may be none today, but all future ChemActivities will likely have assigned problems and reading from a traditional textbook.

ChemActivity 1: Bond Angles and Shape

(What are the bond angles and shape of CH_4?)

Model 1: Planetary Model of an Atom

In a planetary model of an atom, **negatively charged electrons** (–1 each) are arranged around a **positively charged nucleus** (+Z = nuclear charge) in a series of **shells** that look like orbits.

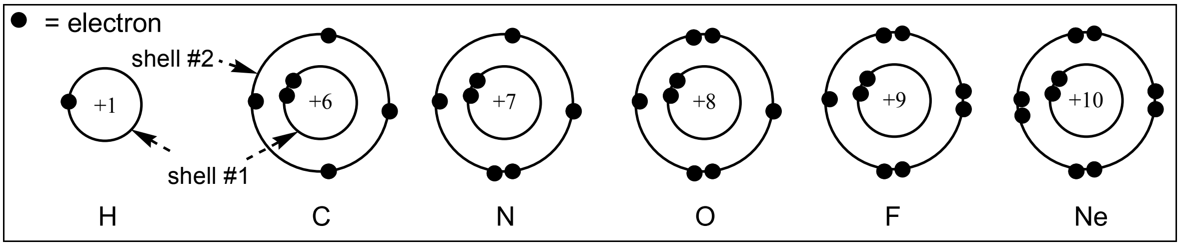


Figure 1.1: Valence Shell Representations of Hydrogen, Carbon, Nitrogen, Oxygen, Fluorine, and Neon

core electrons = electrons in any inner shell(s) (don't participate in bonding)

core atom = the nucleus (made up of protons and neutrons) plus the core electrons

valence electrons = electrons in the outermost shell (participate in bonding)

valence shell = outermost shell, where valence electrons are found

*Electrons **DO NOT** "orbit" the nucleus like the planets orbit the sun. In ChemActivity 3 we will study a more complex model in which electrons are described as inhabiting 3-dimensional regions of space called "orbitals" (1s, 2s, $2p_x$, $2p_y$, $2p_z$, 3s, etc.).*

Critical Thinking Questions

1. (E) What does the number (+Z) at the center of each atom in Figure 1.1 represent, and what number would you expect at the center of a representation of a bromine atom (Br)?

2. (E) How many total electrons does an oxygen atom have, and how could you find the answer to this using a periodic table?

3. (E) How many valence electrons does each atom in Figure 1.1 have, and what number on a periodic table gives you these answers?

4. What is the maximum number of electrons that can fit in…
   a. (E) shell No. 1?
   b. (E) shell No. 2 (Neon has a full Shell No. 2)?
   c. Describe how the answers to a) and b) are contained in the structure of the periodic table.

Model 2: Bonding and Non-bonding Electron Domains

Bonding electron domain = shared valence electrons (2, 4, or 6e^-) localized between two core atoms

3 types → **Single Bond** (1 pair, 2 electrons); **Double Bond** (2 pairs, 4 e^-); **Triple Bond** (3 pairs, 6 e^-)

Non-bonding electron domain (“**lone pair**”) = pair of valence electrons (2 e^-) not involved in a bond

One way to think of a **bond**: **two positively charged core atoms mutually attracted to the negatively charged electrons that are localized between them**.

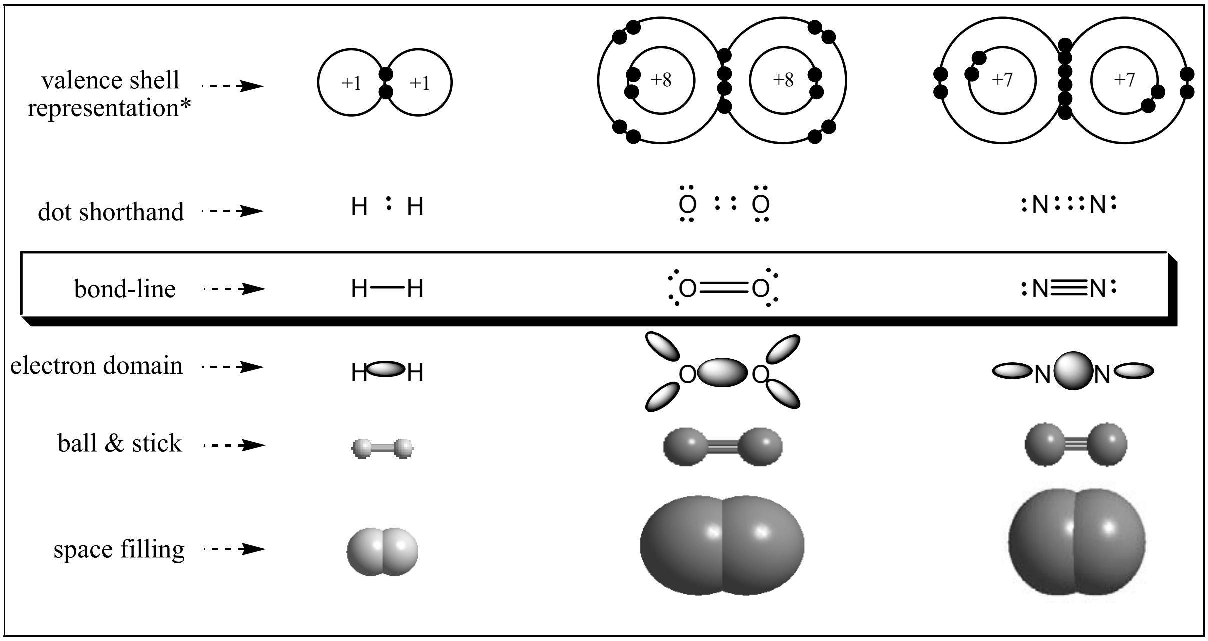


Figure 1.2: Example of a Single, Double, and Triple Bond

Critical Thinking Questions

5. (E) How many electrons are in a triple bond?

6. (E) Identify each **lone pair** shown in the first four rows of Figure 1.2.

7. (E) Each molecule in Figure 1.2 has exactly one bonding electron domain. Identify it and…
    a. label what **type** of bonding electron domain it is.
    b. report the number of electrons in each bonding electron domain.

8. You hear a student from a nearby group say that “E*lectron domains repel one another*.” Cite evidence from Figure 1.2 to support or refute this statement.

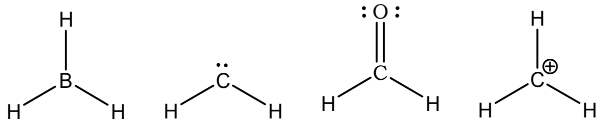
Model 3: Bond Angles

bond angle = angle defined by any three atoms in a molecule. (e.g., ∠HBH in BH_3, below)

According to the Valence Shell Electron Pair Repulsion model (**VSEPR**) **electron domains spread out as far as possible** from one another (repel one another).

Even for a molecule with different-sized electron domains (e.g., H_2CO), bond angles remain very close to those you would expect if all the electron domains were the same size.

Table 1.1: Bond Angles of Selected Molecules

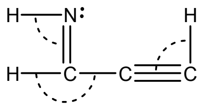
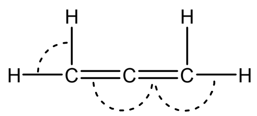
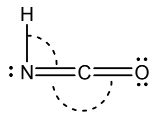
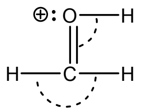
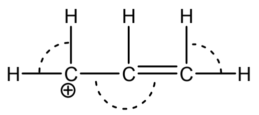
Bond-line Structure	Approximate Bond Angle
$H{-}Be{-}H$ $:N{\equiv}C{-}H$ $\ddot{\underset{..}{O}}{=}C{=}\ddot{\underset{..}{O}}$	180
	120

Critical Thinking Questions

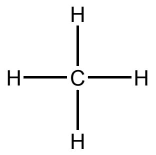
9. Use VSEPR to explain why the ∠HBH bond angle of BH_3 is 120°. (*Hint*: What is one-third of 360°?)

10. Both the ∠HCH and ∠HCO bond angles of H_2CO (formaldehyde) are very close to 120°, but one is slightly smaller than the other. Predict which is smaller, and explain your reasoning.

11. Use VSEPR to assign a value of "**close to 180°**" or "**close to 120°**" to each bond angle marked with a dotted line. (These angles are drawn as either 90° or 180°, but may be another value.)

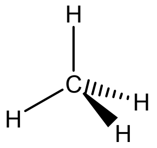






12. Consider the following **flat** drawing of methane (CH_4).



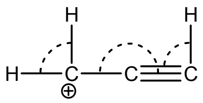
   a. What is ∠HCH bond angle implied by this drawing if you assume it is flat?
   b. Are the electron domains of this flat CH_4 spread out as much as possible?
   c. Use model materials to **make a model of CH_4** (methane). If you assembled it correctly, the four bonds (bonding electron domains) of your model will be 109.5° apart.
   d. In which representation, **the drawing above** or **the model in your hand** (circle one) are the H's of CH_4 more spread out around the central carbon?

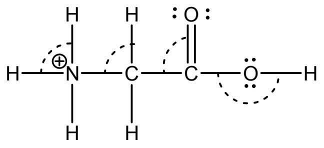
e. Confirm that your model looks like the following drawing. The **wedge bond** represents a bond coming out of the page, and the **dash bond** represents a bond going into the page.

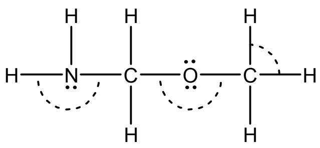


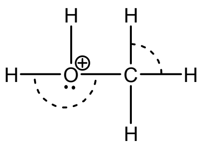
f. You will often see methane drawn as if it were flat (like on the previous page). Why is this misleading, and what is left to the viewer's imagination when looking at such a drawing?

13. Use VSEPR to assign a value of (close to) 109.5, 180 or 120 to each marked **bond angle**.

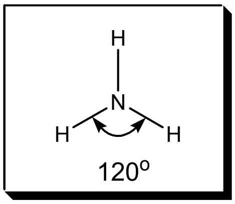




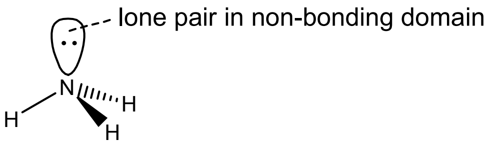




14. A student draws the picture of **ammonia** (NH_3) in the box below, left, and predicts it will be a flat molecule with ∠HNH bond angles of exactly 120°. Unfortunately, the student left something out.



Student's incorrect drawing

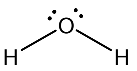


Accurate Representation of Ammonia

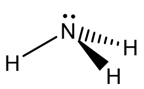
a. What did the student omit from his drawing?

b. What is the actual ∠HNH bond angle of ammonia (based on the drawing above, right)?

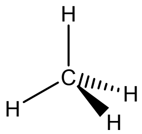
c. Explain why water, ammonia, and methane (shown below) all have about the same bond angles (close to 109.5°) even though they have different numbers of bonds.



water



ammonia



methane

Memorization Task 1.1: Correlation between #No. of Electron Domains and Bond Angle

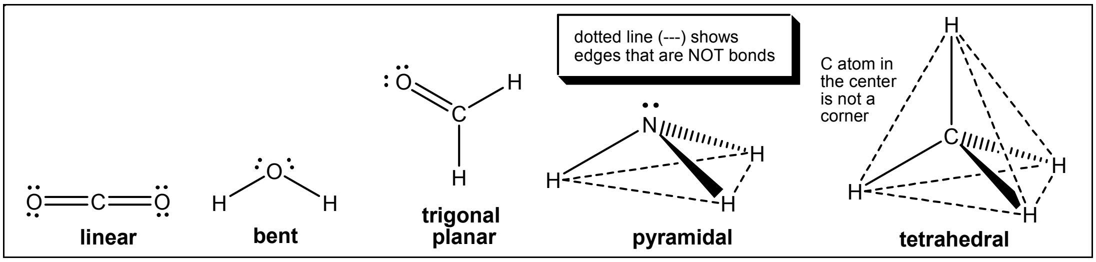
Electron Domains (bonding + non-bonding)	**Bond Angle Close To…**	**Examples**
4	109.5°	CH_4, NH_3, H_2O, H_4N^+
3	120°	BH_3, H_3C^+, CH_2, H_2CO
2	180°	BeH_2, O_2N^+, CO_2, HCN

Model 4: Shape

A **central atom** = an **atom bonded to two or more other atoms**. (e.g., Oxygen in H—O—H)

Each **central atom** has a **shape** determined by the arrangement of the **atoms** attached to it.

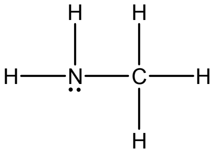
Memorization Task 1.2: The five molecular shapes we will encounter in this course


dotted line (---) shows edges that are NOT bonds
C atom in the center is not a corner
linear
bent
trigonal planar
pyramidal
tetrahedral

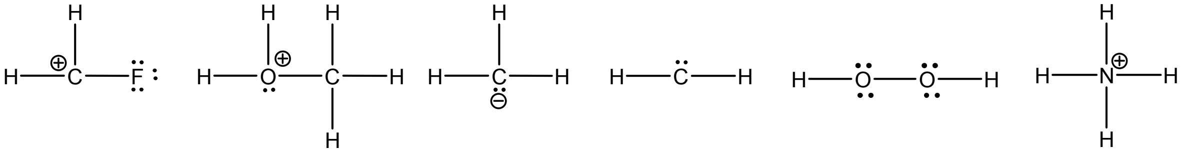
Critical Thinking Questions

15. (E) Explain why the molecule H—F is not associated with an official shape as defined in Model 4.

16. How many central atoms does the molecule H_2NCH_3 have, and what is the shape about each?



17. Indicate the bond angle and shape about each central atom.



18. Explain how there can be two kinds of bent: “**bent-109.5o**” and “**bent-120o**,” and give an example of each from the previous question. (Note that “bent-109.5^{o}” is more common than “bent-120^{o}.”)

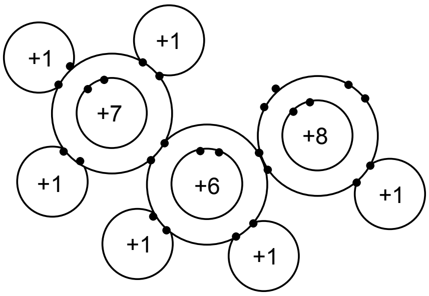
19. A student makes the following statement: “The shape of water is **tetrahedral** because the four electron pairs about oxygen are approximately 109.5^{o} apart and point to the corners of a tetrahedron.” What misconception does this statement convey?

20. A student who missed this class needs to know how to predict the bond angles and shape of a molecule from looking at its bond-line representation. Write a concise but complete explanation for this student.

Exercises

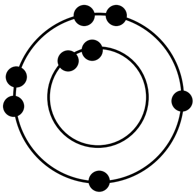
1. Draw a valence shell representation of a
   a. Helium atom.
   b. Sulfur atom.

2. In the box, draw a **bond-line representation** of the molecule shown on the left. Be sure to include only valence electrons (either as line bonds or lone pairs).



line-bond rep.

3. Consider the incomplete valence shell representation below.



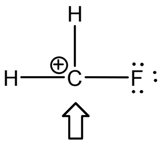
   a. Assume the atom is neutral, and write the correct nuclear charge at the center of the atom.
   b. What is the identity of this neutral atom?

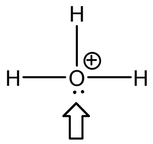
4. How many valence electrons does a neutral
   a. K atom have?
   b. C atom? N atom? O atom?

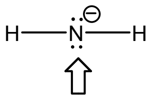
5. Consider the molecules $AlCl_3$ (aluminum chloride) and CF_4 (carbon tetrafluoride).
   a. Draw the valence shell representation of each.
   b. Predict the value of the XYX bond angle, and explain your reasoning.

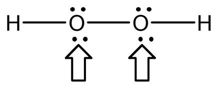
6. Draw an example of a bent molecule with a bond angle of near 109.5 °; then draw a different bent molecule with a bond angle of about 120 °.

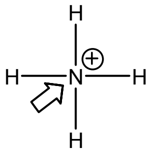
7. Label each atom marked with an arrow with the appropriate **shape name,** and **estimate the bond angles around it** as being close to one of 180°, 120°, 109.5° or 90°. (circled charges indicate the charge on the molecule or fragment)



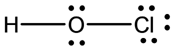


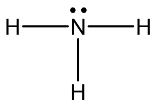


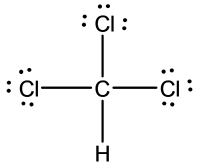


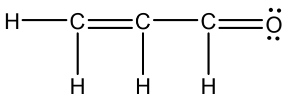


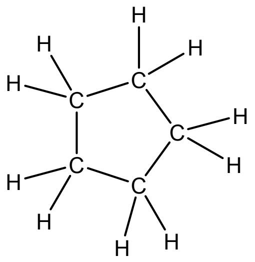
8. Make a model of each of the following molecules:

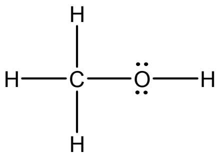


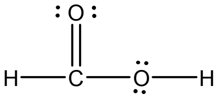


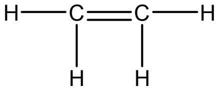


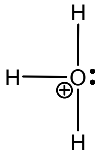












a. Based on your model, draw a bond-line representation with as many atoms as possible in the plane of the paper. Use wedge and dash bonds to represent any atoms that do not lie in the plane of the paper.

b. Indicate each unique bond angle and the shape of each unique central atom.

9. Read the assigned pages in the text, and do the assigned problems.

Using "The Big Picture" & "Common Points of Confusion" Sections

It can be fun to "discover" your own answers as you are asked to do in this workbook, but…

How do you know if your "discovered" understanding is valid?

The answer is: Even practicing scientists and professors never know *for sure* that they are correct. In some ways, deciding if you are right is the hardest part of being a scientist. A practicing scientist cannot "check the key" to see if her new theory is correct! In this course and in real life you must constantly test and improve your current understanding by applying it to problems and discussing it with peers. One goal of this course is to develop the ability to recognize the signs when you are correct; and equally importantly, recognize the signs when you are missing something critical.

After completing a ChemActivity, one way to start checking your understanding is to read the Big Picture and Common Points of Confusion sections (examples on the next page). If the homework or these sections do not make sense to you then you are missing something important. You need to go back and study the activity, do more problems, read the textbook more closely, or seek help from a peer, teaching assistant or your instructor. (More advice about how to know if you are "**learning the right thing**" can be found in the "To the Student" section the precedes the Table of Contents for this book, and the Frequently Asked Questions section of the IntroActivity that precedes this chapter.)

The Big Picture

After this week you will rarely be asked to report a bond angle or shape. Yet it is critical that you be able to do both. Doing well in organic chemistry largely depends on your ability to see molecules as three-dimensional objects. The electrons of most every central atom you will encounter are arranged 109.5 ° or 120 ° apart (180° arrangements are quite rare), but it gets complex when you are expected to see a molecule with multiple central atoms in 3D. The purpose of this activity is to get you started thinking about tetrahedral and trigonal planar geometries. If you do not already have a model set, borrow or purchase one. You will need it for the first half of this course while you are "programming" your brain to see the two-dimensional drawings on the page as 3D objects.

Common Points of Confusion

At the end of each chapter you will find a brief explanation of common student misconceptions. This section may be useful if a homework problem does not make sense or as final preparation for a quiz.

- When asked the question, "What is the **shape** of water?" students sometimes answer "tetrahedral" because they know that the four electron domains of water spread out into a tetrahedral-type pattern. However, the answer is "bent" because shape is determined by the location of the atoms. Similarly, it makes no sense to ask what is the bond angle between the two lone pairs of water—there should be approximately 109.5° between these lone pairs, but this is difficult to measure.
- Some students mistakenly assume they are expected to predict the EXACT **bond angle** of a given molecule. Generally, you are expected to predict only if the bond angle is closest to 180, 120, or 109.5 degrees.

ChemActivity 2: Lewis Structures

(How do I draw a legitimate Lewis structure?)

Model 1: G. N. Lewis' Octet Rule

In the early part of the last century, a chemist at the University of California at Berkeley named Gilbert N. Lewis devised a system for diagramming atoms and molecules. Though simple, the system is still used today because predictions made from these diagrams often match those based on experiment.

Lewis proposed the following representations for the first ten elements with their **valence electrons**.

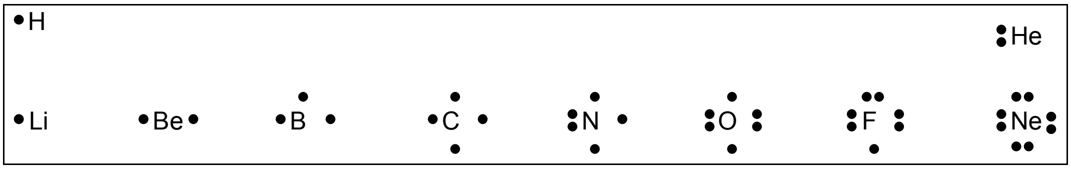


Figure 2.1: Electron Dot Representations of Elements

Only He and Ne are found in nature as shown above. All the other elements are found either as a charged species (**ion**) or as part of a **molecule** that can be represented as a legitimate **Lewis structure**.

CHECKLIST: a Legitimate Lewis Structure is a dot or line bond representation in which…

I. The correct TOTAL number of valence electrons is shown.

II. The sum of the valence electrons around each hydrogen atom is two.

III. The sum of the valence electrons (bonding pairs + lone pairs) around each **carbon, nitrogen, oxygen, or fluorine atom is eight**–an **octet**. (this is the **"octet rule")**

Note that Lewis' rules apply to H, C, N, O and F. We will find that atoms in the next row of the periodic table (e.g., silicon, phosphorus, and sulfur) and beyond commonly violate the octet rule.

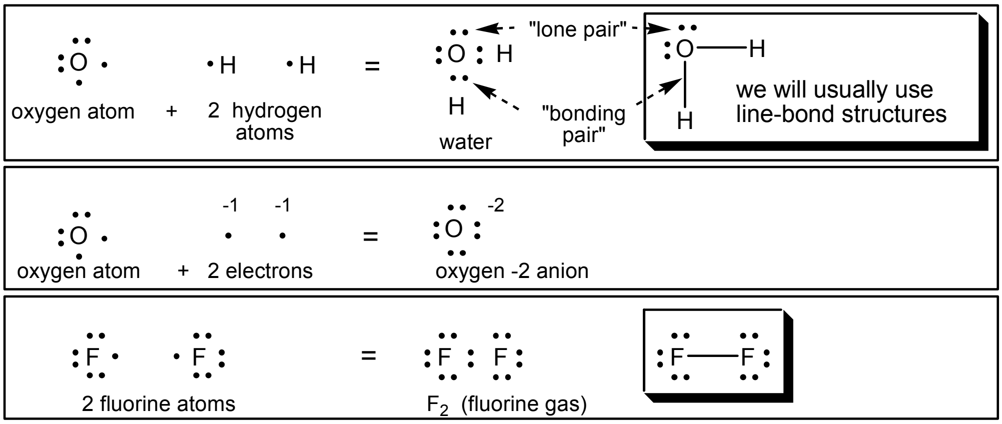


Figure 2.2: Examples of combinations that form legitimate Lewis structures

Read this page once, and begin answering the Critical Thinking Questions on the next page.

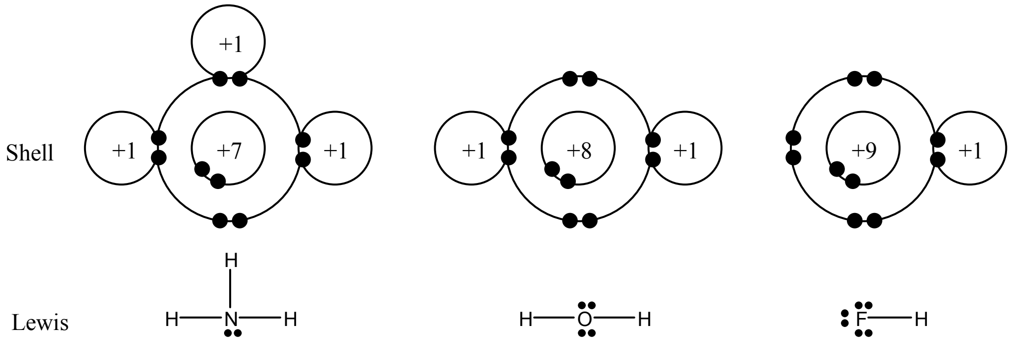


Figure 2.3: Valence Shell and Lewis Representations of Selected Compounds

Critical Thinking Questions

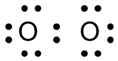
1. (E) Confirm that each molecule or ion in Figures 2.2 and 2.3 is a legitimate Lewis structure.

2. The **valence shell** of an atom in a legitimate Lewis structure (*see* Figure 2.3) has what in common with the valence shell of a noble gas? (Noble gases are stable elements found in the last column of the periodic table, e.g., He, Ne, Ar, etc.)

3. Draw a shell representation and Lewis structure for the ion of fluorine that you predict is most likely to be stable, and explain your reasoning.

4. Draw a Lewis structure of a neutral molecule that you expect to be a stable and naturally occurring combination of one carbon atom and some number of fluorine atoms.

5. The following structure is NOT a legitimate Lewis structure of a neutral O_2 molecule.



   a. Explain why it is not legitimate.

   b. Which item on the legitimate Lewis structure CHECKLIST in Model 1 is violated?

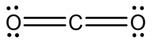
6. It is impossible to draw a legitimate Lewis structure of a neutral NH_4 molecule. Hypothetically, how many valence electrons would such a neutral NH_4 molecule have *if it could exist*?

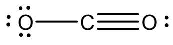
   a. The +1 cation, NH_4^+, does exist. How many valence electrons does one NH_4^+ ion have?

   b. Draw the Lewis structure for NH_4^+

7. Describe how to calculate the total number of valence electrons in a +1 ion, in a -1 ion.

Model 2: Two Lewis Structures for CO_2


I


II

Experiments indicate that both carbon-oxygen bonds of carbon dioxide (CO_2) are identical.

Critical Thinking Questions

8. (E) Are both structures of carbon dioxide (CO_2) in Model 2 legitimate Lewis structures?

9. (E) Which Lewis structure best fits experiments indicating that both C to O bonds are identical?

Model 3: Formal Charge

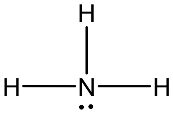
One of the Lewis structures of CO_2 in Model 2 is less favored because it has an imbalance of charge. To find the "hot spots" of + and – charge in a structure we must calculate the formal charge of each atom.

Memorization Task 2.1: Formal Charge = (Group Number) – (no. lines) – (no. dots)

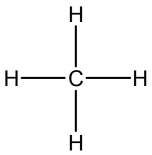
- **Group Number** = Column number on the periodic table (or number of dots on atom in Fig. 2.1)
- **No. lines** = Number of line bonds to the atom in the structure
- **No. dots** = Number of non-bonded electrons on an atom in the structure

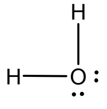
Critical Thinking Questions

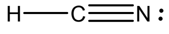
10. (E) According to the periodic table at the end of this book, what is the **Group Number** of nitrogen?
    a. (Check your work.) Does this match the number of dots on N in Fig. 2.1?
    b. (E) How many line bonds are attached to N on the structure of NH_3?
    c. (E) How many nonbonded electrons are drawn on N in NH_3?
    d. Calculate the formal charge of each atom in NH_3?

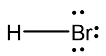


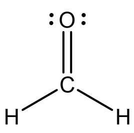
11. (Check your work.) Most atoms in organic molecules (including all atoms of NH_3) have a **zero formal charge**. Confirm that each atom at right has a zero formal charge.



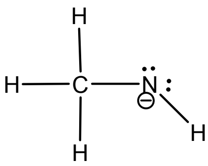


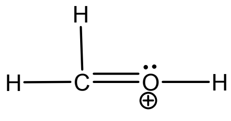


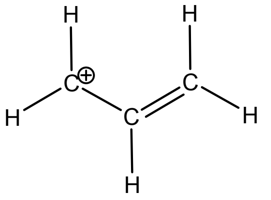


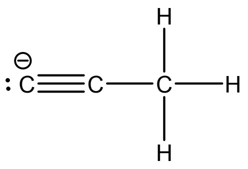


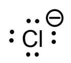
12. In this course we will often encounter **+1 and -1 formal charges**, though rarely will we see formal charges of +2, -2, +3, -3, etc., because they are generally unfavorable. By convention, **only nonzero formal charges are shown on a structure**. Plus 1 and minus 1 formal charges are shown as a + or –or as a circled + or – (⊕ /⊖). Confirm the formal charge assignments below.



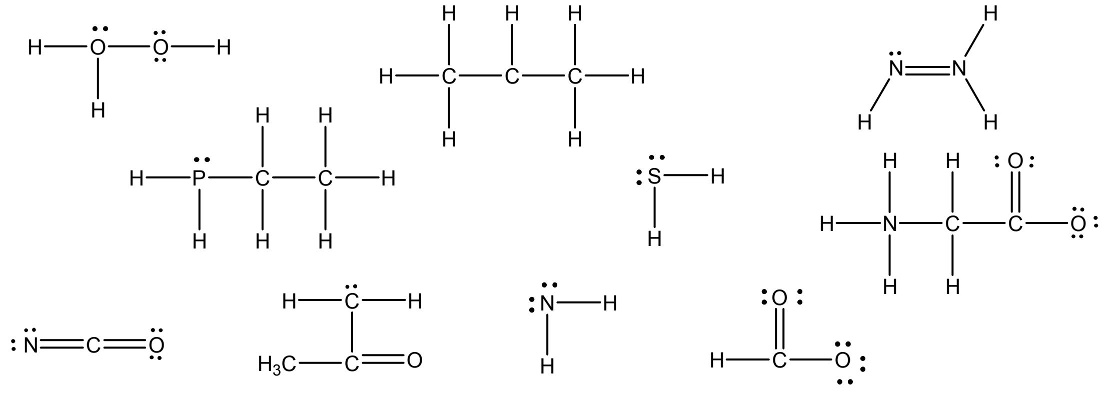








13. A complete Lewis structure must show all nonzero formal charges. Complete each of the following Lewis structures by adding any missing formal charges.



14. **Net Charge** = total charge on a molecule. (Check your work.) Structures in the top row of the previous question have a net charge of +1, structures in the middle row have a net charge of zero, and structures in the bottom row have a net charge of -1.

15. T or F: The sum of the formal charges on a Lewis structure is equal to the net charge on the molecule or ion. (If false, give an example from CTQ 13 that demonstrates this is false.)

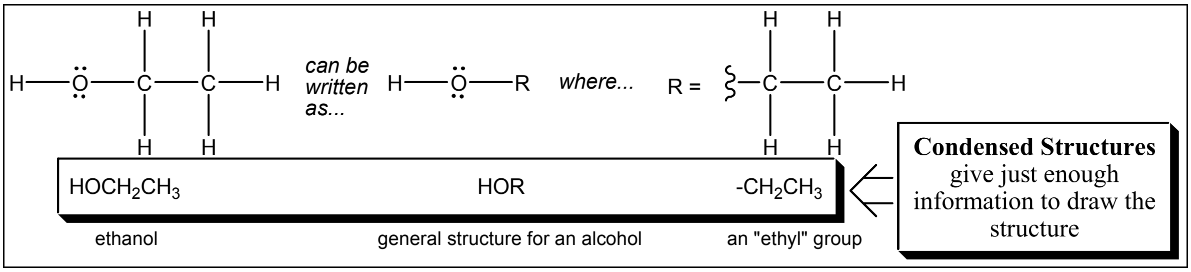
16. T or F: If the net charge on a molecule is zero, the formal charge on every atom in the molecule must equal zero. (If false, give an example from CTQ 13 that demonstrates this is false.)

17. Identify the one Lewis structure in CTQ 13 that is NOT legitimate, and explain what attribute of a legitimate Lewis structure it is missing.

(Check your work.) *The top-center Lewis structure in CTQ 13 is a* ***key exception to the octet rule*** *called a carbocation.* ***We*** *will study carbocations extensively in the course. For reasons we will discuss later, a carbocation carbon rarely is involved in a double or triple bond. That is, a carbocation almost always has three single bonds, as shown on the next page.*

Model 4: Condensed Structures and Using R, X, & Z as Placeholders

R, X, and Z are not elements but placeholders for atoms or groups of atoms. For example, ethanol…

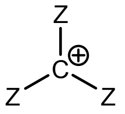
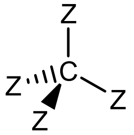
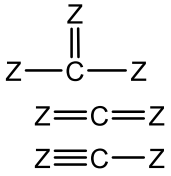
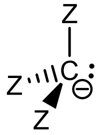
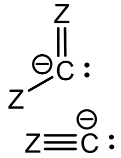
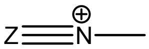
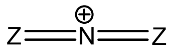
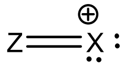
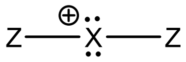

can be written as...
where...
R =
$HOCH_2CH_3$
HOR
$-CH_2CH_3$
ethanol
general structure for an alcohol
an "ethyl" group
Condensed Structures give just enough information to draw the structure

Memorization Task 2.2: Conventions for the use of R, X, and Z as placeholders

- **R** is used to represent H or an **alkyl group.** An alkyl group is a straight or branched chain made from C and H atoms with formula C_nH_m e.g., $-CH_3$, $-CH_2CH_3$, $-C(CH_3)_3$, etc.
- **X** is used to represent F, Cl, Br, or I (the common "halogens")
- **Z** will be used to represent *any* atom or group of atoms

If the identity of R, X, or Z is not specified, assume a wide range of legal identities are possible.
For example: in the table below, the formal charges shown hold true regardless of the identities of Z.

Model 5: Recognizing Formal Charges for C, N, O, and X

	+1	0	−1
C	 Note: The two other ways to draw a carbocation are very uncommon.	 	 
N	  four ways (**draw the two that are missing**)	draw three ways	draw two ways
O	draw three ways	draw two ways	draw one way
X	  two ways (less common)	draw one way	draw one way (an anionic atom)

Critical Thinking Questions

18. Complete the box in Model 5 for N^{+1}, by drawing the *other* two ways an N can carry a +1 formal charge. (*Hint*: These two structures should have molecular formulas $^{+}NZ_4$, and $^{+}NZ_3$, respectively.)

19. Complete the rest of the table for N, O or X by drawing the number of Lewis structures specified.

20. For a legitimate Lewis structure…

    a. What is the formal charge of **any** nitrogen with four bonds? … three bonds? … two bonds?

    b. What is the formal charge of **any** oxygen with three bonds? … two bonds? … one bond?

    c. What is the formal charge of **any** halogen (X) with two bonds? … one bond? … zero bonds?

21. Parts a-c in the previous CTQ mean you can quickly recognize the formal charge on an N, O and X without considering non-bonded electrons (dots). Explain why a similar statement equating formal charge and number of bonds DOES NOT WORK **for carbon** (i.e., you have to look for the dots).

Memorization in Organic Chemistry:

Memorization is a small but important part of learning organic chemistry. **Memorization Tasks** such as the one below will be clearly marked throughout this book. This is done to encourage you to memorize the critical bits of information *in* these boxes AND help you realize that you can derive everything *outside* of these boxes from the key concepts in the ChemActivity.

Memorization Task 2.3: Corrleation between No. of bonds and formal charge for C, N, O, X

Before the next class: Study the patterns in Model 5, and do practice problems until you can QUICKLY recognize the formal charge (+1, 0, or -1) of any C, N, O or X in a structure without counting.

For example, an N with four bonds should look "wrong" without a +1 formal charge; and an N with two bonds should look "wrong" without a -1 formal charge. (Write a similar rule for oxygen!)

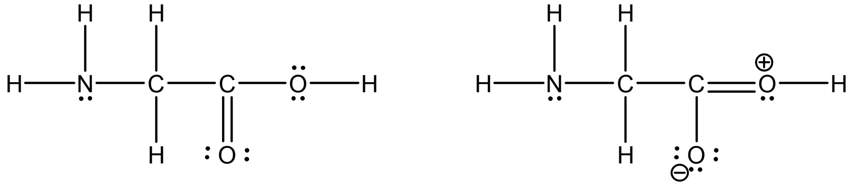
Note that for carbon you must count the number of bonds AND check whether there is a lone pair on C. That is, a C with three bonds and no lone pair should look "wrong" without +1 formal charge; and a C with three bonds and one lone pair should look "wrong" without a -1 formal charge.

Exercises

1. Make a checklist that can be used to determine if a Lewis structure is correct and that it is the best Lewis structure.

2. Turn back to Model 2, and add any missing formal charges to each Lewis structure of CO_2.
   a. Based on the concept of formal charge, which is the better Lewis structure for CO_2 (in Model 2), Lewis structure I or Lewis structure II? Circle one, and explain your reasoning.
   b. Is your choice consistent with the experimental data?

3. Shown below are two possible Lewis structures for the amino acid called glycine.



Structure I Structure II

   a. Predict the ∠COH bond angle based on the Lewis structure on the left.
   b. Predict the ∠COH bond angle based on the Lewis structure on the right.
   c. Which prediction do you expect to be more accurate? Explain your reasoning.

4. Draw the Lewis structure of a neutral molecule that is a naturally occurring combination of hydrogen atoms and one sulfur atom. What is the shape of this molecule?

5. Draw legitimate Lewis structures of the following species, and predict the geometry about the central atom (shape).

a. NH_3
b. NO_2^+
c. N_2O (try with N or O as the central atom)
d. CCl_4
e. CO_3^{2-}
f. N_2 (Note: based on the definition, a molecule with only two atoms does not have a shape.)

6. For each element, predict (and draw a Lewis structure of) the most commonly occurring ion (some of these have a charge greater than +/- 1)

a. sulfur
b. iodine
c. magnesium
d. oxygen

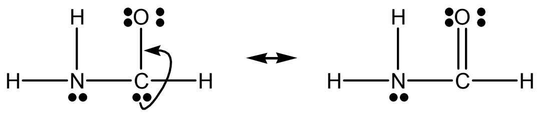
7. Predict which of the following species is least likely to exist.

CH_2 NO^+ HO^-

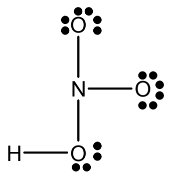
8. The molecules BH_3 and SF_6 and the ion SO_4^{2-} exist and are stable. Draw a Lewis structure of each, and comment on whether they are exceptions to Lewis' octet rule.

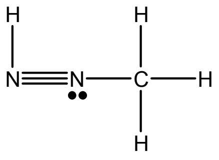
9. These are NOT legitimate Lewis structures (and are missing formal charges). Show (as in the example) how a pair of electrons can be moved to make the Lewis structure legitimate.

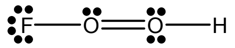
(curved arrow shows where the electron pair was moved from and to)



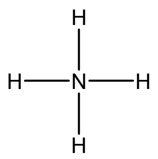
legitimate Lewis structure



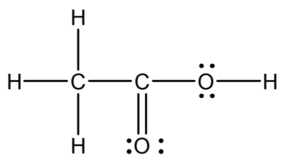




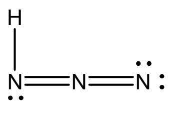
10. Fill in missing formal charges where needed (all lone pairs are shown).

a) 

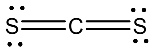
NH_4^+

b) 

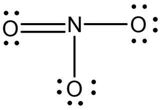
CH_3COOH

c) 

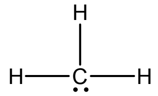
HN_3

d) 

CS_2

e) 

NO_3^-

f) 

CH_3^-

11. Below each structure in the previous question is a "condensed structure" that tells you something about how the atoms are arranged. Draw complete Lewis structures for each of the following condensed structures. (The net charge, if any, on each molecule is given at the end.)

    a. $CH_3CH_2^{-}$

    b. CH_2CH_2

    c. CH_2CCH_2

    d. $C(CH_3)_3^{+}$

    e. BH_4^{-}

    f. NCO^{-}

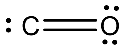
    g. CH_2OH^{+}
    (two different acceptable answers)

    h. $CH_2CHCHCHCH_2^{+}$ which may also be written as $CH_2(CH)_3CH_2^{+}$
    (more than one acceptable answer)

12. For each structure in the previous two questions, predict the shape of each central atom.

13. Carbon monoxide (CO) is an example of an overall neutral molecule (net charge = 0) that has non-zero formal charges. Draw a Lewis structure of carbon monoxide (CO).

14. Explain why this Lewis structure for CO is not as valid as the Lewis structure you drew in the previous question even though it has no "hot spots" of + or – charge (formal charges).



15. Give an example of a molecule appearing in this activity that is an exception to the octet rule. (Remember that the octet rule applies only to C, N, O and F.)

16. The following questions refer to the table in Model 5.

    a. Is there a box that has N with three bonds and no lone pairs?

    b. Is there a box that has O with three bonds and no lone pairs?

    c. Explain why the following is true: To determine the formal charge of a carbon in a structure you must consider *both* the number of bonds AND whether there is a lone pair, whereas for N or O you need count only the bonds.

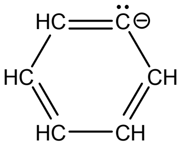
17. Carbon is a little strange in that it does not always follow the octet rule. We will learn about this later in the course. For now know that:

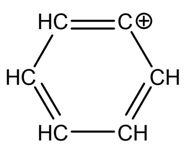
    - C with three bonds and a lone pair must have a –1 formal charge.
    - C with three bonds and no lone pair must have a +1 formal charge.

    a. Draw an example of a molecule containing a carbon with a –1 formal charge.

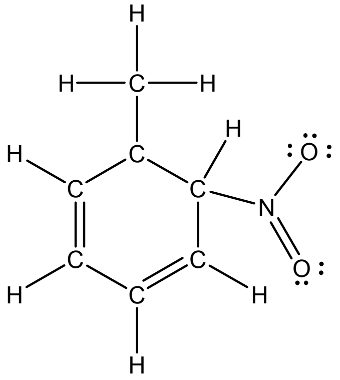
    b. Draw an example of a molecule containing a carbon with a +1 formal charge.

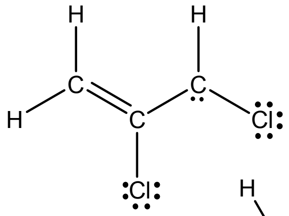
18. Which of the following ions are you more likely to encounter in this course? Explain your reasoning

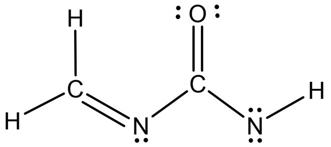


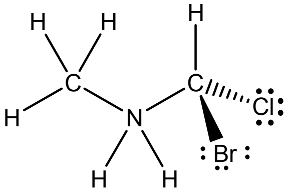


19. Complete each Lewis structure shown below.









20. Read the assigned pages in your text, and do the assigned problems.

The Big Picture

Checking for an octet and assigning a formal charge can be done by counting, but this is very slow. These operations must become second nature so that you can quickly determine **formal charge** and use this information to answer a higher-level question. Students who fail to familiarize themselves with the common occurrences of C, N, O, and X with +1, 0, and –1 formal charges shown in Model 5 quickly find themselves falling behind their classmates at this critical juncture in the course. Things get more complex quickly, so invest some time now and prepare yourself.

Common Points of Confusion

- The number one student error at this point in the course is to confuse the TWO REASONS TO COUNT ELECTRONS on a Lewis structure. One is to check for an octet by looking for eight electrons around an atom. The other is to determine its formal charge by counting bonds for N, O, and X and by counting bonds AND lone pairs for carbon.
- Lewis said that C, N, O, and F must have an octet. (He didn't know about carbocations.) The fact that third-row elements like sulfur and phosphorous can expand their octets is not a violation of Lewis' **octet rule**.
- Carbon is the only atom among C, N, O, or F that can exist without an octet. This is because it is the least electronegative of the four. In other words, N, O and F are so electron-greedy that they will never accept having only six electrons in their valence shell. The most common of these are called **carbocations.**

ChemActivity 3: Electron Orbitals

(How can you determine the hybridization state of an atom in a given molecule?)

Model 1: Orbital Representation of Shell #No. 2

Electrons are tiny and move very fast, so it is useful to think of them as a mist of negative charge concentrated in a region of space (e.g., in a bond). Organic chemists call this mist an **electron cloud**.

An **orbital** is the three-dimensional region of space where this "**electron cloud**" is likely to be found.

Shell #No. 2 was previously shown as an "orbit" holding up to eight electrons. Here we show it as four **orbitals**: 2*s*, $2p_x$, $2p_y$ and $2p_z$. Each orbital can be **empty** (zero e^-), **half-filled** (one e^-) or **full** (two e^-).

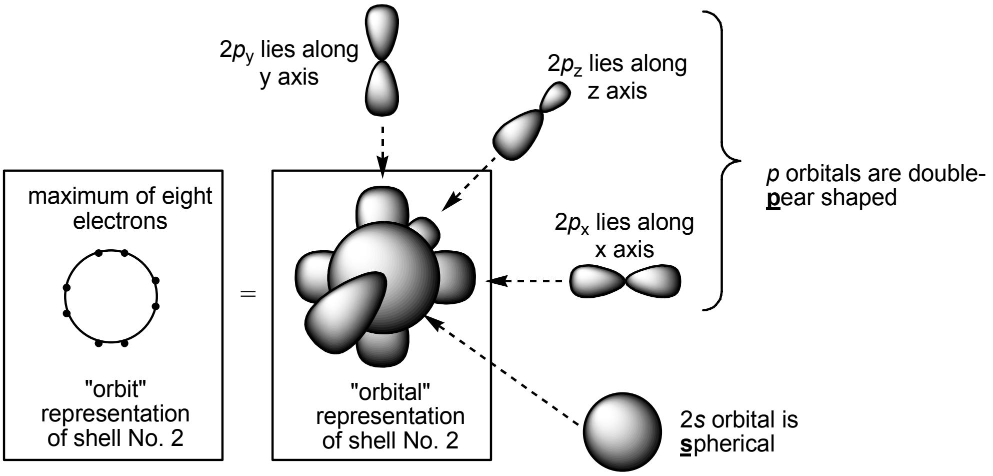

$2p_y$ lies along y axis
$2p_z$ lies along z axis
p orbitals are double-pear shaped
maximum of eight electrons
=
$2p_x$ lies along x axis
"orbit" representation of shell No. 2
"orbital" representation of shell No. 2
2s orbital is spherical

Figure 3.1: Orbit and Orbital Representations of Shell #No. 2.

Critical Thinking Question

1. (E) What is the maximum number of electrons that can fit in a single **orbital** (2*s*, $2p_x$, $2p_y$ or $2p_z$)? (Is your answer consistent with the capacity of Shell #No. 2 based on the orbit representation?)

Model 2: Electron Configuration

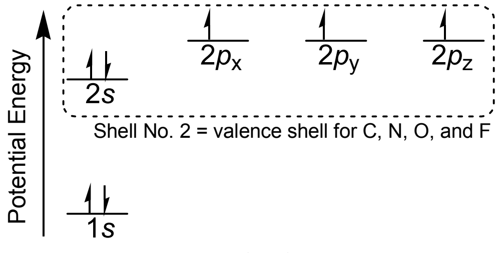


Figure 3.2: Electron Configuration Diagram

In previous courses you may have seen electrons (represented as up or down arrows) assigned to orbitals on an **electron configuration diagram** like Figure 3.2.

An electron in a 2*s* orbital is lower in potential energy than an electron in any of the three 2*p* orbitals because the territory of an *s* orbital is closer (on average) to the nucleus than that of a *p* orbital. A 1*s* orbital is so low in energy that it is not considered part of the valence shell.

Critical Thinking Questions

2. What neutral atom is represented by the electron configuration in Figure 3.2?

Model 3: Sigma (σ) Bonds and Pi (π) Bonds

A bond is formed by an overlap of orbitals. We will encounter two types of bonds in this course: **head-to-head overlaps called (σ) sigma bonds, and side-to-side overlaps called (π) pi bonds**. (Most often, a bond is an overlap of two half-filled orbitals. This gives two electrons per bond.)

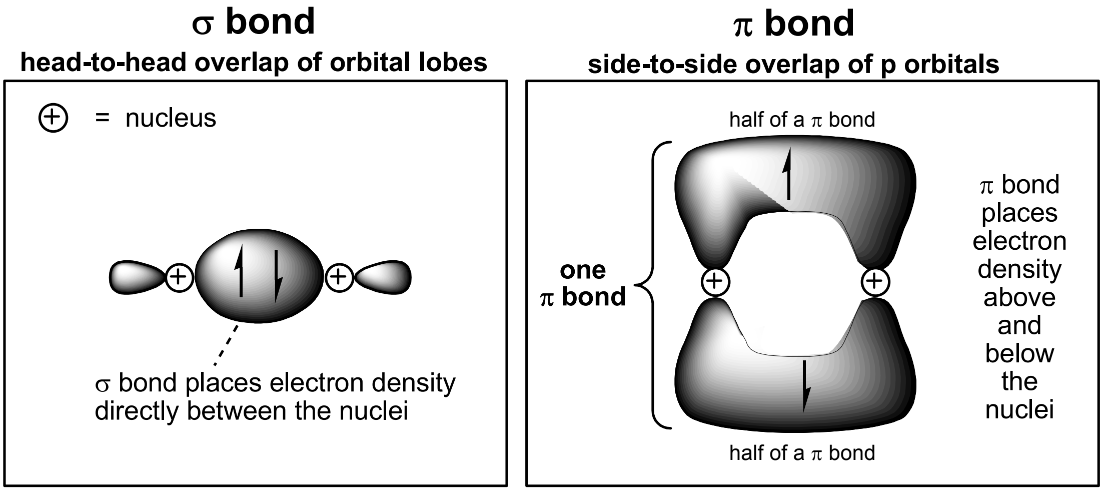
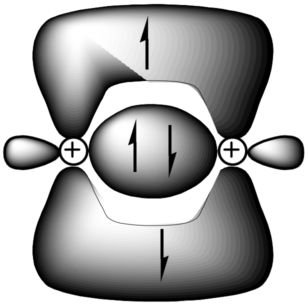

σ bond
head-to-head overlap of orbital lobes
⊕ = nucleus
σ bond places electron density directly between the nuclei
π bond
side-to-side overlap of p orbitals
half of a π bond
one π bond
π bond places electron density above and below the nuclei
half of a π bond

Figure 3.3: σ and π Bonds

- **single bond** = one σ bond
- **double bond** = one σ bond *plus* one π bond
- **triple bond** = one σ bond *plus* two π bonds

Critical Thinking Questions

3. A student says the picture at right must represent a triple bond.



   a. Agree or disagree with this statement, and explain your reasoning.

   b. How many electrons are there in a triple bond, and how many electrons are there in the bond represented at right?

   c. What misconception may have caused this student to think this was a representation of a triple bond?

   d. You are supposed to imagine that an orbital is a 3D object like a balloon. In the picture of a double bond above, all the "balloons" are centered in the plane of the paper. Where is there space to add a second π bond linking these same two nuclei so as to generate a triple bond?

Model 4: 109.5°, 120°, and 180°-Hybrid Orbital Sets

You may have noticed a problem: The $2p_x$, $2p_y$ and $2p_z$ orbitals in Model 1 are 90° apart from one another, and so do not point in the right directions to make 109.5°, 120°, or even 180° bond angles.

To solve this "problem" double Nobel Prize winner (1954, Chemistry; 1962, Peace) and Caltech and Stanford professor Linus Pauling invented orbitals he called **hybrid orbitals,** which pointed in the right directions. There are three **hybrid orbital sets**, one to explain each family of experimentally observed bond angles: close to **109.5°**, close to **120°**, and close to **180°**.

Demonstration 1: Derivation of the 109.5°-Hybrid Orbital Set

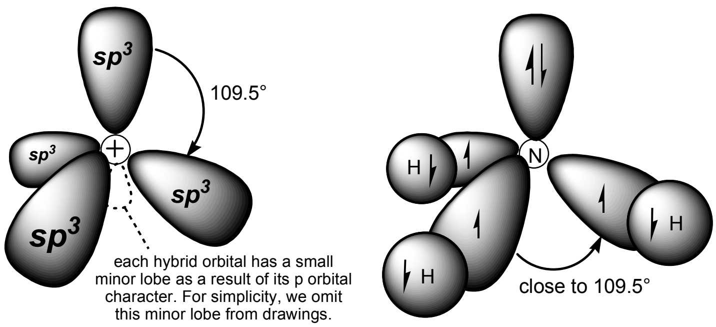
- Make a play-dough model of each orbital in Shell #No. 2 (one red sphere = **2*s***; and three green double-pear-shaped pieces = **$2p_x$, $2p_y$ and $2p_z$**), and mix them together to form a large brown ball.
- Cut this ball into four equal pieces representing four identical "mixed" or "hybrid" orbitals.
- Spread these four **hybrid orbitals** as far apart as possible about the center (109.5° apart).

Critical Thinking Questions

4. Consider any one of the four identical hybrid orbitals in the 109.5° set.
   a. What fraction of the clay in this hybrid orbital was originally red (came from the 2*s* orbital)?
   b. What fraction of the clay in this hybrid orbital was originally green (came from a 2*p* orbital)?
   c. Explain the name "***s*(1/4)–*p*(3/4) hybrid orbital**" for each of the four orbitals.
   d. In fact, each of the four hybrid orbitals in the 109.5° set is called an ***sp^3*-hybrid orbital**. Explain the name "**sp^3-hybrid orbital**."

Model 5: Hybrid Orbital Picture of Bonding in Ammonia

Any central atom with bond angles close to 109.5° is ***sp^3*-hybridized** (uses 109.5°-hybrid orbital set)

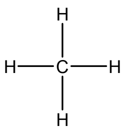
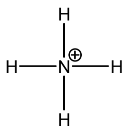
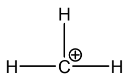
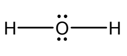
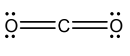
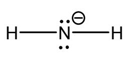
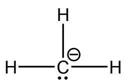
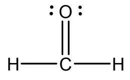
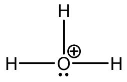

sp3
109.5°
sp3
+
sp3
sp3
each hybrid orbital has a small minor lobe as a result of its p orbital character. For simplicity, we omit this minor lobe from drawings.
N
H
H
H
close to 109.5°

109.5° Hybrid Orbital Set **Representation of Ammonia**

Figure 3.4: sp^3-Hybridized Nitrogen in Ammonia

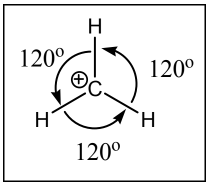
Critical Thinking Questions

5. Circle each central atom that you expect to be sp^3-hybridized.

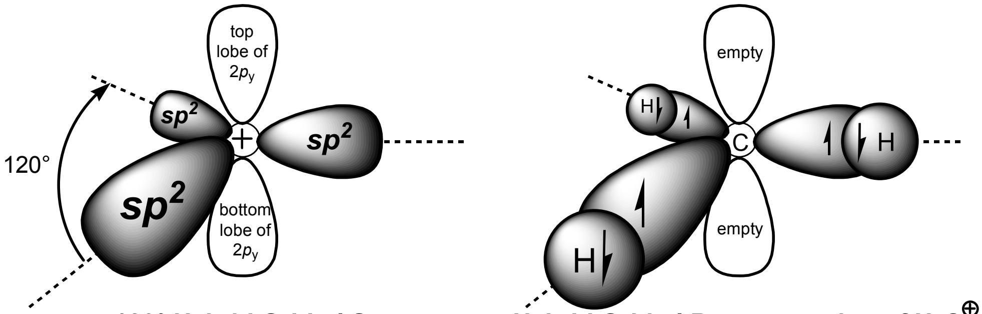










Demonstration 2: Derivation of the 120°-Hybrid Orbital Set

A 109.5°-hybrid orbital set was needed to explain the 109.5° bond angles of NH_3, H_2O, etc. Similarly, a 120°-hybrid orbital set is needed to explain 120° bond angles such as those of $H_3C^{\oplus}$ (*shown below*).



- **Put aside *one p* orbital** (usually $2p_y$)
- Mix the remaining three orbitals: $2s$ (red clay), $2p_x$ and $2p_z$ (green clay) to form a brown disk in the x-z plane
- Cut this disk into three equal **hybrid orbital** lobes, and point them away from one another (120° apart)



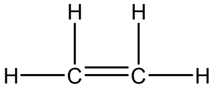
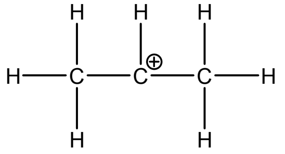
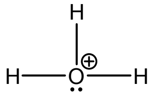
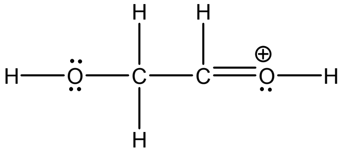
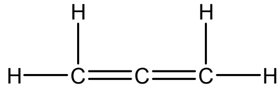
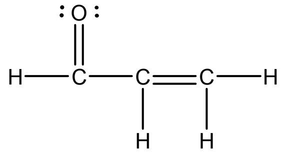
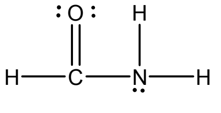
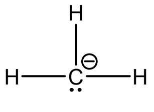
120° Hybrid Orbital Set **Hybrid Orbital Representation of $H_3C^{\oplus}$**

Figure 3.5: sp^2-Hybrid Orbital Set and an Example of an sp_2-Hybridized Carbon

Critical Thinking Questions

6. Construct an explanation for why each hybrid orbital in the 120°-hybrid orbital set is called an **sp^2-hybrid orbital**. (Note that the 120°-hybrid orbital set is also called the sp^2-hybrid orbital set.)

7. Circle each central atom you expect to be ***sp^2*-hybridized**.

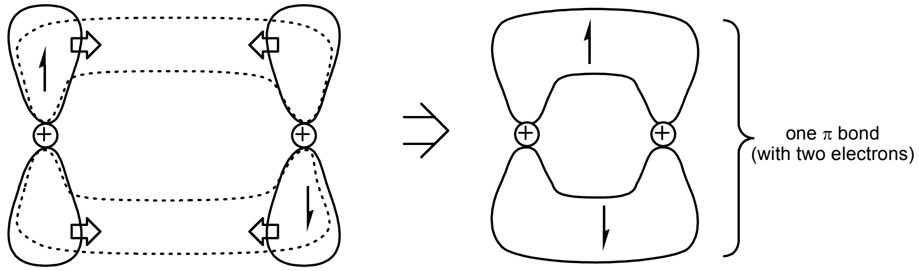
8. Fill in the blank: Each C—H σ bond in Figure 3.5 is formed by overlap of a ______ orbital and an sp^2-hybrid orbital. (Identify one such orbital overlap C—H bond that appears in Figure 3.5.)

9. (E) How many total valence electrons are found in the cation $H_3C^{\oplus}$?

10. (E) How many of these valence electrons are located in the *p* orbital of $H_3C^{\oplus}$ in Figure 3.5?

Model 6: Orbital Description of a Double Bond

Recall that side-on overlap of two half-filled **p orbital**s results in a π bond.



Orbital overlap between two ***sp^2*-hybridized atoms** can result in a **σ bond *and* a π bond**…

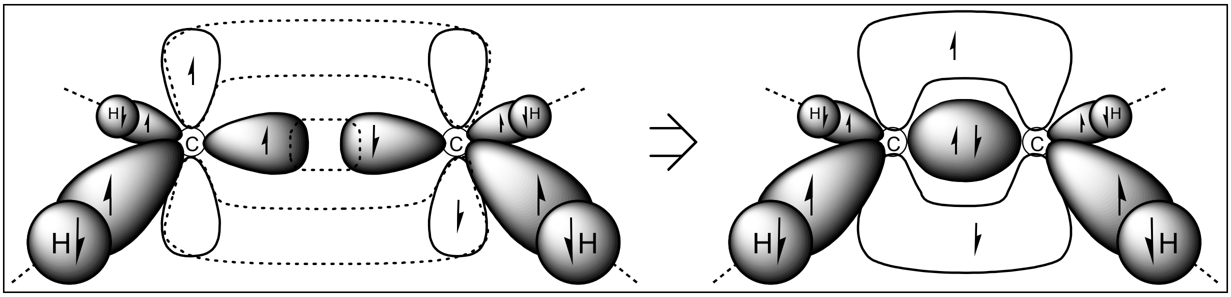


Figure 3.6: Orbital Representation of a Double Bond

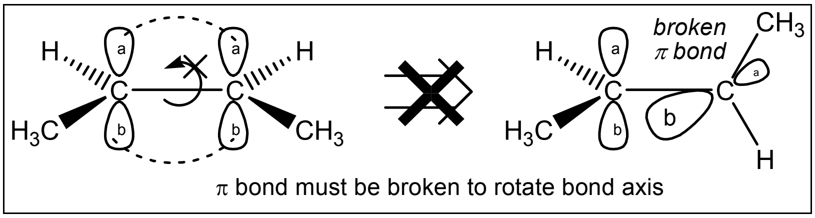
Critical Thinking Questions

11. On the left side of Figure 3.6, label the areas shown with a dotted line where…
    a. one σ bond can form.
    b. one π bond can form.

12. Draw a Lewis structure of the molecule represented with orbitals on the right side of Figure 3.6.

13. Label the σ and π bond on both the Lewis structure you just drew and the orbital representation on the right side of Figure 3.6.

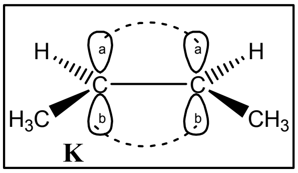
Memorization Task: Single bonds can freely rotate, but double bonds cannot…



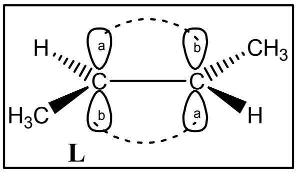
π bond must be broken to rotate bond axis

…because the π portion of a double bond prevents the bond axis from rotating.

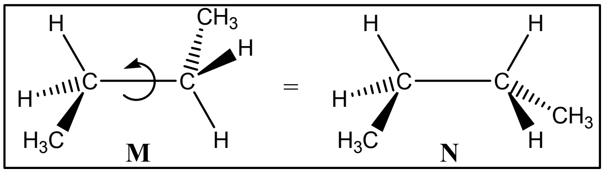
14. Construct an explanation for why structures K and L are different molecules while M and N are two representations of the *same* molecule.



K



L



M **N**

Model 7: Orbital Description of a Triple Bond

To make a play-dough **180°-hybrid orbital set**…

- Put aside ***two*** *p* orbitals ($2p_x$ and $2p_y$)
- Mix the remaining orbitals: 2*s* (red) and $2p_z$ (green) to make a sausage that lies along the z axis.
- Cut this sausage into two ***sp*-hybrid orbitals**, and point them in opposite directions (180° apart).

sp-hybridized = atom with 180° bond angles (employs the 180° (*sp*) hybrid orbital set)

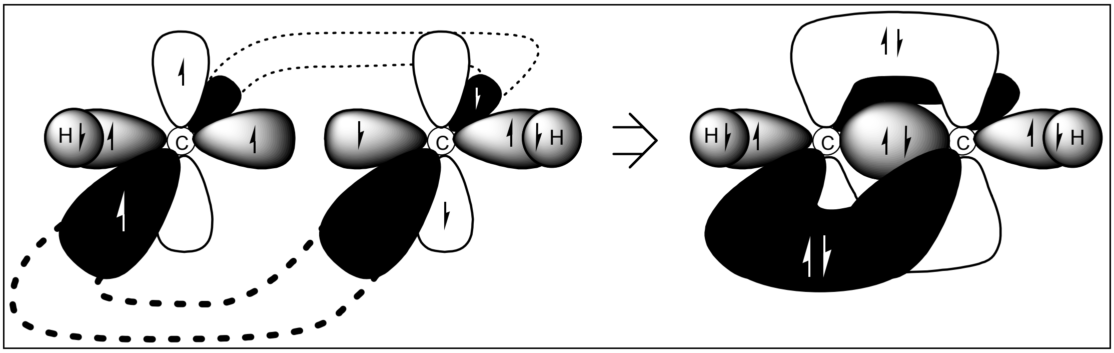


Figure 3.7: Orbital Representation of a Triple Bond

Critical Thinking Questions

15. On the left side of Figure 3.7, dotted lines are used to show the π bond that can form between the two **black** *p* orbitals.

    a. (E) Add dotted lines showing where the π bond can form between the two white *p* orbitals.

    b. (E) Add dotted lines showing where the σ bond can form. (Hint: See Figure 3.6)

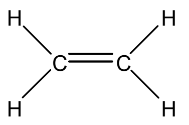
16. Now consider the fully formed molecule on the right side of Figure 3.7.

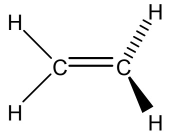
    a. Draw a Lewis structure of this molecule.

    b. Identify orbital representations of the two π bonds and three σ bonds in Figure 3.7, and match these with representations of bonds on the Lewis structure you just drew.

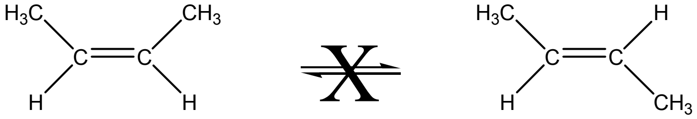
Exercises

1. Explain why the representation of ethene on the left is more accurate than the one on the right.





2. Explain why the two molecules below cannot inter-convert without breaking the π portion of the double bond.

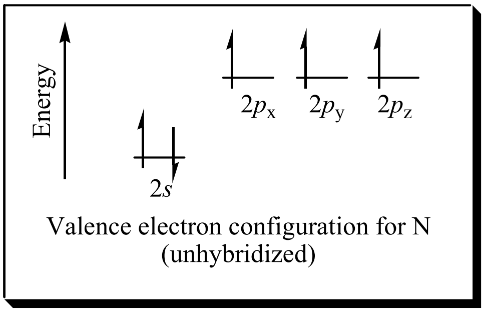


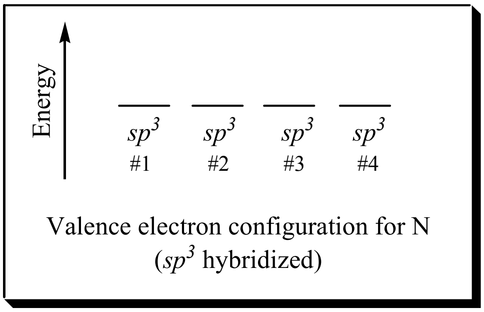
3. The diagram below left shows the energies and electron occupation of the valence orbitals of nitrogen using the standard set (2*s*, $2p_x$, $2p_y$ and $2p_z$).

   a. Explain why the potential energies of all four sp^3-hybrid orbitals are the same.

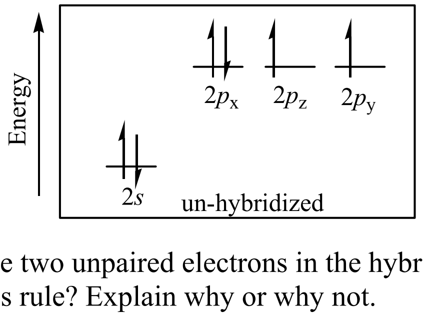
   b. Construct an explanation for why the energy level line for an sp^3-hybrid orbital is placed three-quarters of the way between the line for 2*s* and the line for each 2*p* orbital.

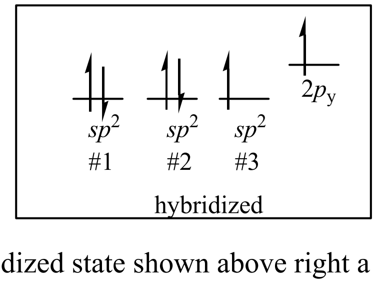
   c. Complete the diagram below right by adding electrons to the energy diagram of sp^3-hybridized N. Be sure to follow Hund's rule, which says: For orbitals of similar energy, half-fill each orbital before filling any one orbital.





   d. What second-row element is shown below, and what hybridization state is shown on the right?

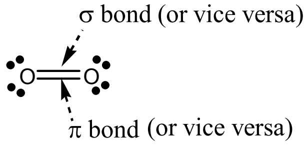




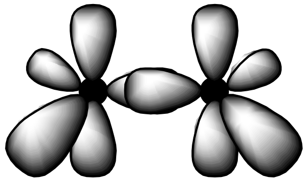
   e. Are the two unpaired electrons in the hybridized state shown above right a violation of Hund's rule? Explain why or why not.

4. Consider the incomplete orbital representation of O_2, below right.
   - a. Identify which lobes are hybrid orbitals (identify the type) and which lobes are *p* orbitals.
   - b. Use dotted lines to show any π bonds.
   - c. Use up or down arrows to show electron occupation of each hybrid orbital or bond.

A double bond consists of one σ overlap and one π overlap.

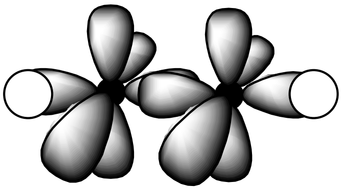


Lewis Drawing of O_2



Orbital Drawing of O_2

5. Consider the following orbital representation of HCCH (ethyne).



Orbital Drawing of

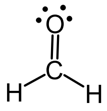
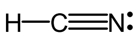
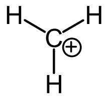
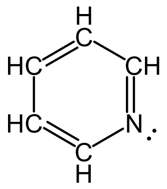
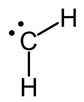
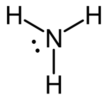
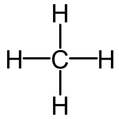
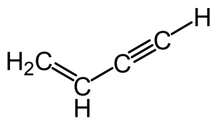
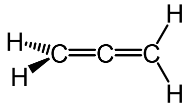
$H-C\equiv C-H$

   - a. Answer the same three questions (a-c) from the previous exercise.
   - b. Label each C–H σ bond in the drawing above.
   - c. What is the total number of σ bonds found in ethyne? …. π bonds?
   - d. How many *p* orbitals are there on a single carbon of ethyne?
   - e. How many hybrid orbitals are there on a single carbon of ethyne?

6. Summarize how one determines the hybridization (also called **hybridization state**) of an atom in a molecule.

7. Explain what is wrong with each of the following statements.
   - a. "A π bond is a double bond."
   - b. "A π bond consists of four electrons, one in each of the four *p* orbitals involved in the π bond."
   - c. "A π bond is twice as strong as a σ bond because it consists of two orbital overlaps instead of just one."

8. For the following structures, indicate…
   a. the hybridization state of each nonhydrogen atom (sp, sp^2 or sp^3)
   b. the number of p orbitals contributed to the system by each nonhydrogen atom.
   c. for each p orbital, label it “**empty**” or “**half-full and involved in a π bond**.”
   (later in the course we will encounter special molecules that can have a “full” p orbital)
   d. the type of hybrid orbital that each lone pair resides in.

9. Report the total number of sigma and pi bonds in each molecule in the previous question.

10. Complete the following tables, and memorize their contents.

Syntax for Naming of Hybrid Orbitals

Old Name of Orbital	Hybrid Orbital is a Mixture of…	New Name of Orbital
$s(1/2)$–$p(1/2)$ orbital	1 part s orbital; 1 part p orbital	“s^1p^1 orbital” or “sp orbital”
$s(1/3)$–$p(2/3)$ orbital		or
$s(1/4)$–$p(3/4)$ orbital		or

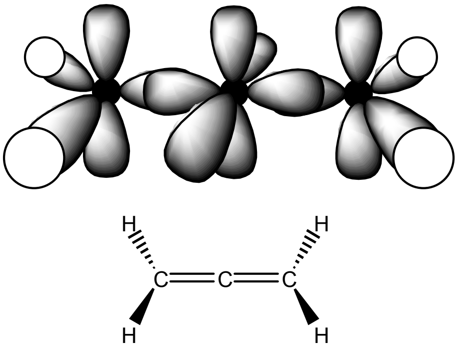
Summary Description of Hybrid Orbital Sets

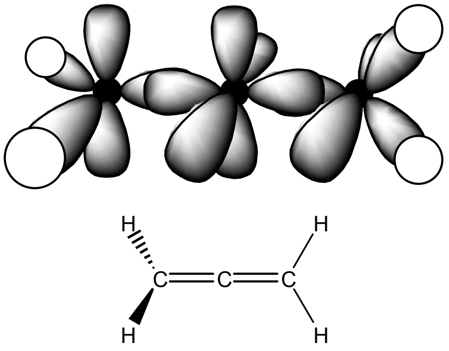
Name of Hybrid Orbital Set	#No. of p Orbitals left untouched in Set	#No. of Hybrid Orbitals in Set	Angle Between Hybrid Orbitals in Set	Example of Atom Employing Set (hybridization state)
sp- or 180° - hybrid orbital set				C in HCCH or Be in BeH_2 (sp-hybridized)
sp^2- or 120°- hybrid orbital set				C in H_2CCH_2 or B in BH_3 (sp^2-hybridized)
sp^3- or 109.5°-hybrid orbital set				C in CH_4, N in NH_3, O in H_2O (sp^{3-}hybridized)

11. Draw orbital representations of bonding in water and methane (CH_4) similar to that of ammonia in Figure 3.4.

12. Draw electron configuration diagrams for carbon in an unhybridized, *sp*^{3}-hybridized state, *sp*^{2}-hybridized state, and *sp*-hybridized state.

13. Construct an explanation for why the representation of CH_2CCH_2 on the right is more accurate.





14. Read the assigned pages in your text and do the assigned problems.

The Big Picture

It may help to remember that hybridization is an invention—a sort of very elaborate analogy—put together by a very clever person (Pauling) to explain bond angles in organic molecules. When we can we will invoke hybridization arguments to extend this analogy; for example, we will use hybridization arguments to explain why some C—H bonds are easier to break than others.

Do not get too attached to one person's description of an atom (e.g., Lewis' or Pauling's), or ask which one is TRUE when they contradict one another. Each one is the imperfect creation of a person who started out in room like this learning about descriptions of atoms and molecules invented by people who came before *them*. Lewis and Pauling invented their models to make better predictions about how atoms and molecules behave. Each is at times useful. Each will at times fall short. Perhaps some day someone in *this* room will think of a model that becomes a textbook standard like Pauling's hybridization model or Lewis' electron-dot model.

Common Points of Confusion

- Many students find **orbitals** to be a bit strange, and for good reason. For example, how can an electron in a *p* orbital simultaneously exist in both lobes? The answer is related to the fact that electrons are so small that they behave like light. That is, they can be considered both a particle and a wave. This strange result (and in fact the origins of orbitals) comes from a branch of physical chemistry that deals with the physics of the very small called **quantum mechanics**. While we will not be studying quantum mechanics in this course, we will occasionally have to deal with the fact that electrons can behave like waves.

ChemActivity 4: Polar Bonds, Polar Reactions

PART A: BOILING A LIQUID TO FORM A GAS

(How is the structure of a molecule related to its melting point or boiling point?)

Model 1: Covalent Bonds vs. Intermolecular Forces

In the previous ChemActivities we have explored **covalent bonds** (e.g., C—H, C—F, O—H, etc.), which are **strong attractive forces** that hold atoms together to form molecules.

Now we will explore the comparatively **weak attractive forces** that make molecules clump together to form a liquid or solid. These are called **intermolecular forces** (some books call them van der Waals forces). The word "**forces**" is used to distinguish them from their much stronger counterparts, "**bonds**."

*Unfortunately, by convention the strongest of these intermolecular forces are called "**hydrogen bonds**." Watch out for this!*

To summarize:

- **Covalent Bonds** = strong attractions between atoms (e.g., O and H) within a molecule (e.g., H_2O)
- **Intermolecular Forces** = weak attractions between separate molecules (e.g., two H_2O molecules)

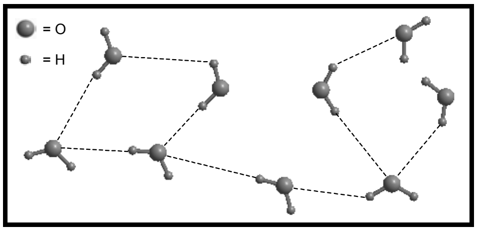


Figure 4.1: Molecular View of Liquid Water

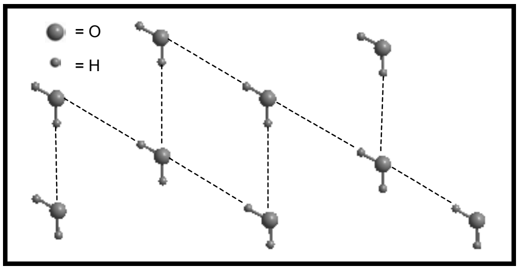


Figure 4.2: Molecular View of Solid Water (ice)

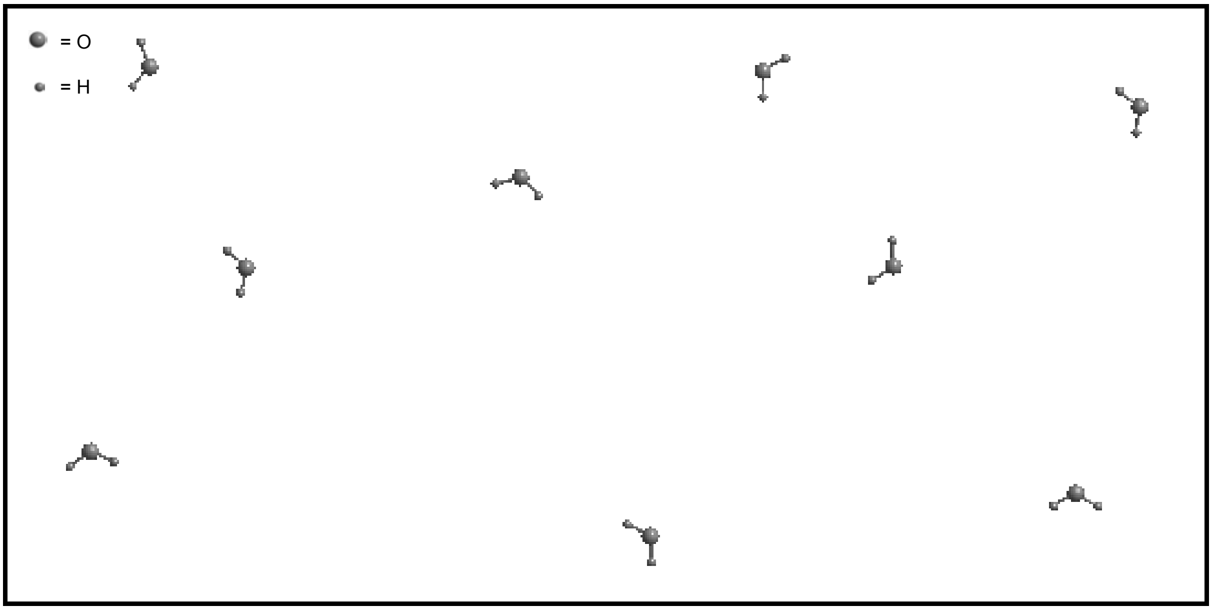


Figure 4.3: Molecular View of Gaseous Water (water vapor or steam)

Read the Model once through and begin answering the CTQ's on the next page.

Critical Thinking Questions

1. (E) What common molecule is represented nine separate times in each Figure in Model 1?

2. Figure 4.1 is a cartoon depiction of liquid water at the molecular level.
   a. (E) Label at least one representation of a **covalent bond** and at least one representation of an **intermolecular force** found in Figure 4.1.
   b. (E) Which are shorter and stronger: covalent bonds or intermolecular forces [circle one]?

3. According to Model 1, in going from liquid water to gaseous water…
   a. What percentage of the O—H **covalent bonds** were broken?
   b. What percentage of the **intermolecular forces** were broken?

Model 2: Polar Bonds

The **H—H** bond is called a **nonpolar bond** because the bonding electrons are shared equally.

H—F is an example of a **polar bond**. Fluorine has a much higher core charge than hydrogen, and so the F atom pulls the bonding electrons toward itself and away from the H atom.

Note: C and H have slightly different affinities for electrons, but because these affinities are very close, **organic chemists consider a typical C—H bond to be nonpolar.**

An **ionic bond** such as in NaCl is the extreme case of a polarized bond. The Na atom has a very low affinity for electrons and completely gives up its share of the bonding electrons to the Cl.

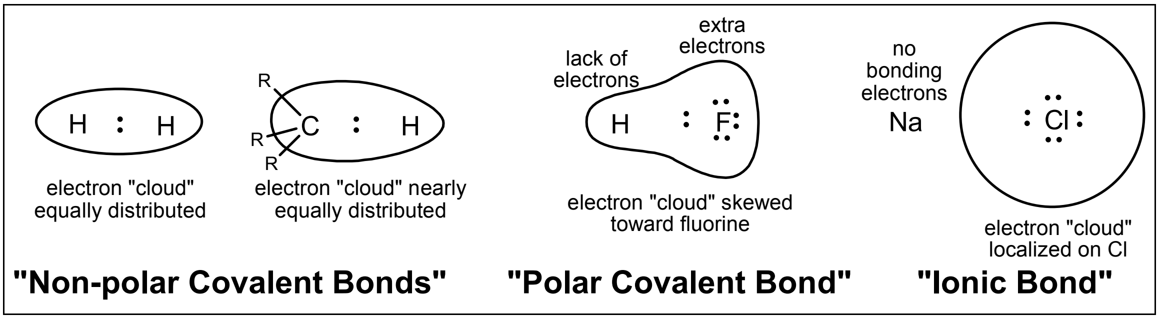

H : H
electron "cloud" equally distributed
R
R
R
C : H
electron "cloud" nearly equally distributed
lack of electrons
extra electrons
H : F:
electron "cloud" skewed toward fluorine
no bonding electrons
Na
: Cl :
electron "cloud" localized on Cl
"Non-polar Covalent Bonds"
"Polar Covalent Bond"
"Ionic Bond"

Figure 4.4: Map of Electron Density for H_2, HF, and NaCl

Organic chemists think of electrons in a bond as forming a fine mist of negative charge. This "**electron cloud**" can assume many different shapes. When this cloud is mapped (as in Figure 4.4) the atom with more "electron mist" near it is said to have a greater **electron density**.

Critical Thinking Questions

4. On the map of electron density for NaCl, add a ⊕ to one atom and a ⊖ to the other indicating the formal charge on each atom.

5. In H—F, neither H nor F holds a full formal charge of +1 or -1. Organic chemists represent a partial charge using the Greek letter delta (δ). On the electron density map of the molecule H—F above, add a δ+ to one atom and a δ– to the other to indicate which way the bond is **polarized**.

Model 3: Electronegativity (EN) and Dipole Moment

The **electronegativity** (EN) of an atom is a measure of its ability to attract electrons toward it and can be used to predict the polarization of a bond in a molecule. In this book, we will deal almost exclusively with the shaded elements.

Table 4.1: Electronegativities (EN) of Elements in the First Five Rows of the Periodic Table

H 2.1																	He
Li 1.0	Be 1.6											**B 2.0**	**C 2.5**	**N 3.0**	**O 3.5**	**F 4.0**	Ne
Na 0.9	Mg 1.2											**Al 1.5**	**Si 1.8**	**P 2.1**	**S 2.5**	**Cl 3.0**	Ar
K 0.8	Ca 1.0	Sc 1.3	Ti 1.5	V 1.6	Cr 1.6	Mn 1.5	Fe 1.8	Co 1.9	Ni 1.9	Cu 1.9	Zn 1.6	Ga 1.6	Ge 1.8	As 2.0	Se 2.4	**Br 2.8**	Kr
Rb 0.8	Sr 1.0	Y 1.2	Zr 1.4	Nb 1.6	Mo 1.8	Tc 1.9	Ru 2.2	Rh 2.2	Pd 2.2	Ag 1.9	Cd 1.7	In 1.7	Sn 1.8	Sb 1.9	Te 2.1	**I 2.5**	Xe

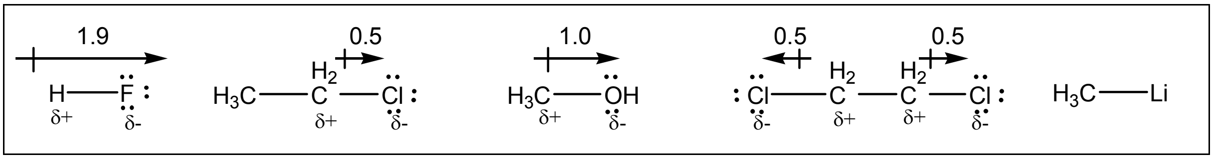


Figure 4.5: Dipole Moments and Calculated EN Differences for Selected Bonds

The polarity of a bond is often represented with a **dipole moment** arrow. The tail is crossed to make a + sign to remind you the head of the arrow points to the more negative end (the end with more electrons).

The size of the arrow is proportional to the **EN difference** = |EN of atom one – EN of atom two|.

Critical Thinking Questions

6. (E) Calculate the EN difference for the C—Li bond in H_3CLi
   a. (E) Add the missing dipole moment arrow to the structure of H_3CLi in Figure 4.5.
   b. (E) Add δ+ and δ– to the C and Li as appropriate.
   c. In what way does the C in H_3CLi differ from all the other carbons found in Figure 4.5?

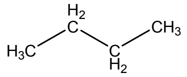
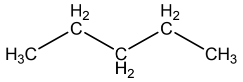
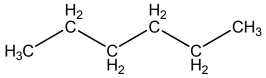
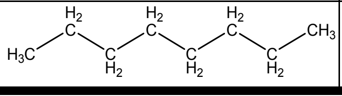
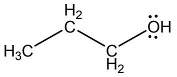
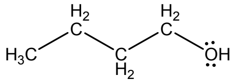
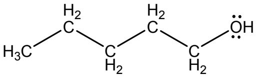
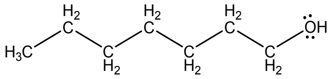
7. Summing all bond dipole moments for a structure gives the molecule's **net dipole moment**. If this net dipole moment is zero, the molecule is overall **nonpolar**. (We will not be doing fancy vector calculations in this course, but be on the lookout for symmetrical molecules whose bond dipole arrows cancel each other.) Circle the only overall nonpolar molecule shown in Figure 4.5.

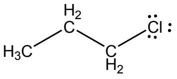
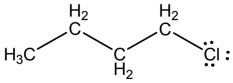
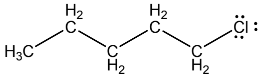
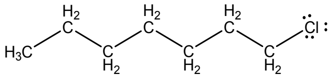
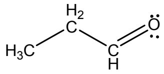
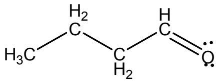
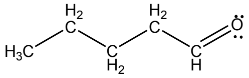
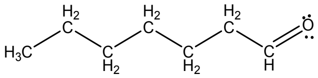
Model 4: Boiling Points

Recall that **intermolecular forces** are the weak attractive forces that cause molecules to clump together into liquids or solids and keep them from drifting apart and becoming a gas.

These forces often can be overcome by just a small amount of heat. The more heat required to overcome the intermolecular forces, the higher the **boiling point** of that compound.

Table 4.2: Boiling Point (bp) Data for Selected Organic Liquids

Name	Structure	bp
Alkanes:		
butane		0.5°C
pentane		36
hexane		69
octane		126
Alcohols:		
1-propanol		97
1-butanol		117
1-pentanol		137
1-heptanol		176

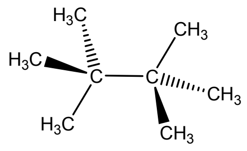
Name	Structure	bp
Alkyl Chlorides:		
1-chloro propane		46°C
1-chloro butane		78
1-chloro pentane		108
1-chloro heptane		160
Aldehydes:		
propanal		48
butanal		75
pentanal		103
heptanal		153

Critical Thinking Questions

8. (E) Table 4.2 is blocked off into sections. Above the name of each section, briefly describe what molecules within that section have in common with other molecules in that same section.

9. Within any one section of Table 4.2, boiling points trend with what physical property?

Information

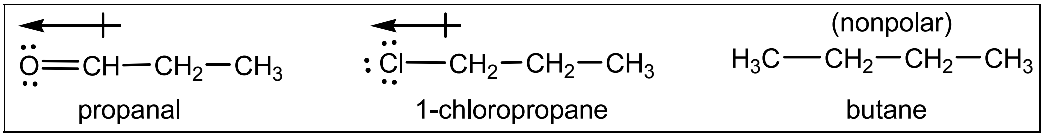


2,2,3,3-tetramethylbutane

It turns out that surface area is more important than molecular weight for predicting boiling point. The larger the **surface area** of a molecule, the more chance it has of sticking to (or even wrapping around) neighboring molecules.

For example: octane has a much higher bp than 2,2,3,3-tetramethylbutane → (bp 107°C), even though they have the same molecular formula.

10. Consider the following three molecules with similar surface areas (from Table 4.2):



a. Based on bp data from Table 4.2, which molecule makes the weakest intermolecular attachments to neighboring molecules in a liquid state?

b. Does dipole moment (polarity) trend with boiling point for these three molecules?

11. Consider the following cartoons of a **polar liquid** and a **nonpolar liquid**. (**$R = CH_2CH_2CH_3$**)

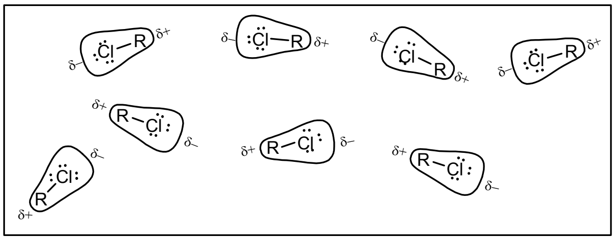


Figure 4.6: Cartoon of a Polar Liquid (1-chloropropane)

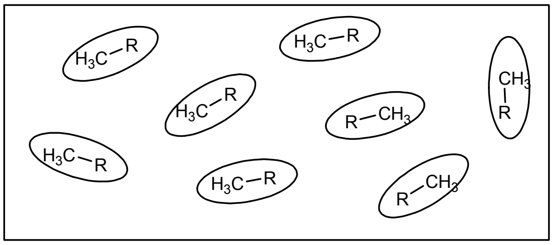


Figure 4.7: Cartoon of a Nonpolar Liquid (butane)

a. For the polar liquid, draw a dotted line connecting each δ+ charge to a nearby δ– charge.

b. Construct an explanation for why you must heat 1-chloropropane to 46°C to initiate boiling (boiling = rapid conversion from the liquid to the gas state) while butane boils at 0.5°C.

Model 5: [Dipole-Dipole] vs. [*Induced* Dipole-*Induced* Dipole] Forces

The intermolecular attractive forces you added to Figure 4.6 are called **dipole-dipole forces**.

Nonpolar molecules like butane do not have dipoles and so do not experience dipole-dipole forces.

To understand how a nonpolar chemical can be a liquid, consider that electron clouds are not fixed. Random fluctuations cause an electron cloud to slosh about like water in an unsteady tub.

Critical Thinking Questions

12. In Figure 4.8, the electron cloud on the left-most butane molecule is shown as having just sloshed to the right, generating momentary partial charges. Use a solid line to show what the new, disturbed electron clouds might look like on each successive butane molecule moving to the right across Figure 4.8.

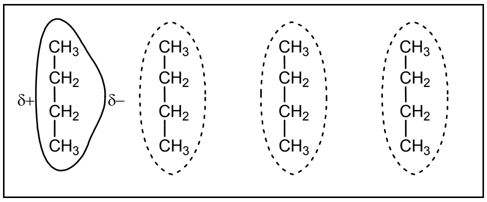


Figure 4.8: Attractive Forces in Butane

13. The attractive forces that hold **nonpolar** molecules together in the liquid state are called "***induced* dipole-*induced* dipole**" attractive forces. Construct an explanation for this name, and compare them to the **dipole-dipole** attractive forces experienced by polar molecules in Figure 4.6.

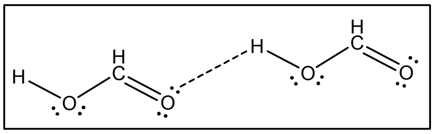
PART B: H⊕ TRANSFER REACTIONS

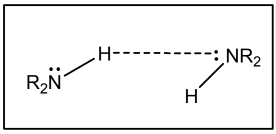
(What happens when intermolecular forces between two molecules are super strong?)

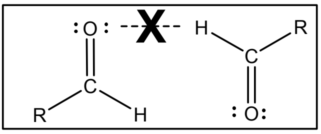
Model 6: Hydrogen Bonding

The dotted lines in Figures 4.1 and 4.2 represent the strongest type of dipole-dipole attractive force called a **hydrogen bond**. A typical hydrogen bond is about 5% as strong as a typical covalent bond.

Hydrogen bonds will normally form *only* between a **[lone pair on N, O, or F]** and an **[H on N, O, or X]** For example:





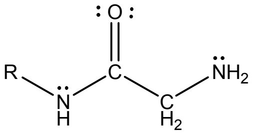


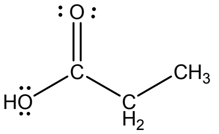
Critical Thinking Questions

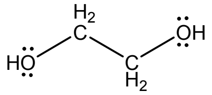
14. (E) According to the rules in Model 6, is the dotted line marked with an **X** a hydrogen bond?

15. Construct an explanation for why an H attached to an N or O atom can participate in a hydrogen bond (H-bond) while an H attached to a carbon atom cannot.

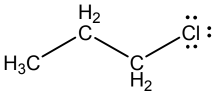
16. Circle each molecule below that you expect to be capable of hydrogen bonding to itself.

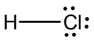


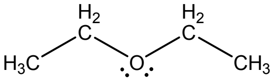


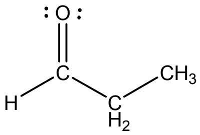


$HOCH_3$









17. An "**hydrogen-bond donor**" has an H suitable for hydrogen bonding. An "**hydrogen-bond acceptor**" has a lone pair suitable for hydrogen bonding.

Only structures in the top row of the previous question are both (and therefore H-bond to themselves!).

Label structures in the bottom row with **H-bond donor, H-bond acceptor**, or **neither**, as appropriate. (Note that only one structure is neither.)

Model 7: Ordinary vs. Extreme H-Bond Donors and Acceptors

Recall that an ordinary H-bond donor will typically share an H with an acceptor, but this H will remain covalently bound to the donor, as shown in Figure 4.9. →

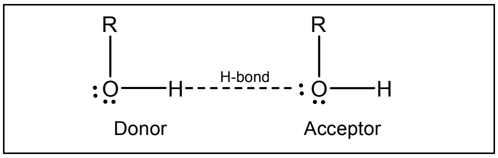


Figure 4.9: Ordinary H-bond Donor and Acceptor

An extreme H-bond donor *or* acceptor will transfer an H^+ (← an H with no electrons) **from donor to acceptor.**

On the next page you will be asked to memorize six common extreme H-bond donors and a working definition of an extreme H-bond acceptor. For now, some examples are provided below.

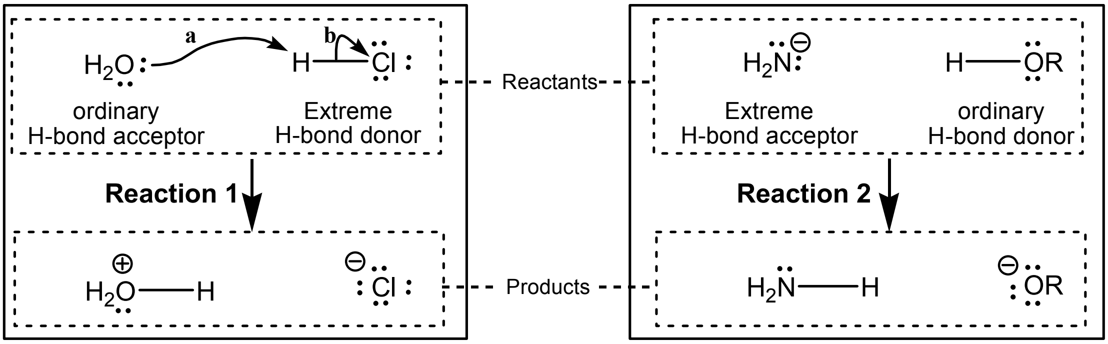


Figure 4.10: H^+ Transfer Reactions Involving an Extreme H-bond Donor or Acceptor

Bond formation and bond breaking for the **H^+ transfer reaction** shown on the left side of Figure 4.10 (Reaction 1) can be represented using two **curved arrows** marked **a** and **b**:

Arrow a says: "One lone pair of electrons on the O (of H_2O) forms a new bond to the H (of HCl)."

Arrow b says: "The electron pair bonding H to Cl breaks from H and becomes a lone pair on Cl $^{\ominus}$."

Critical Thinking Questions

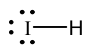
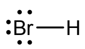
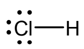
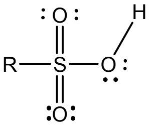
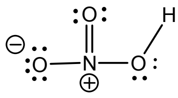
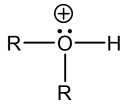
18. (E) For Reactions 1 and 2 in Figure 4.10, label any bond that is "**broken**" among the reactants and any bond that is "**new**" among the products.
19. (E) True or False: An extreme H-bond donor can react only with an extreme H-bond acceptor.
20. Add curved arrows to Reaction 2 in Figure 4.10 showing bond formation and bond breakage.
21. By convention, organic chemists draw their curved arrows from the perspective of the electrons. Write a sentence describing what each of *your* curved arrows says about the electrons in Rxn 2.

Memorization Task 4.1:

By the start of next class, memorize the contents of Tables 4.3 and 4.4 and the definitions of a **strong acid** and a **strong base** on this page.

Strong Acid (e.g., H—Cl) **easily donates an H^+** (previously called an extreme H-bond donor).

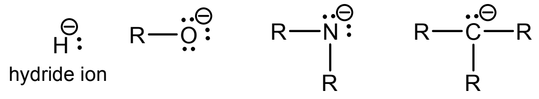
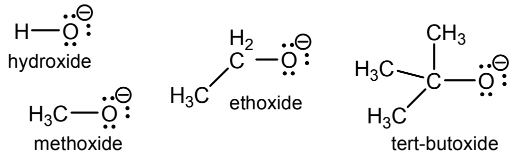
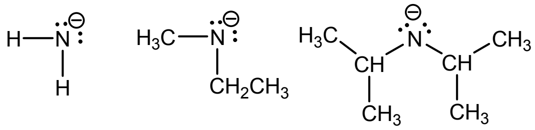
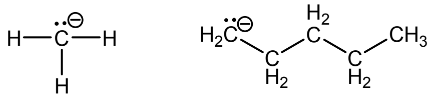
Table 4.3: The Six Strong Acids Used in this Book

Hydroiodic Acid	Hydrobromic Acid	Hydrochloric Acid	Sulfuric Acid (when R = OH)	Nitric Acid*	Hydronium Ion (when R = H)
					

Strong Base (e.g., $H_2N^{\ominus}$) **easily accepts an H^+** (previously called an extreme H-bond acceptor)

Strong Base = molecule with a [lone pair] and [-1 formal charge] *localized** on an H, C, N, or O atom.

Table 4.4: Examples of Common Strong Bases

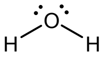
Most strong bases are of the form of one of these generalized structures → where R = H or alkyl group [C_nH_m]	
Oxygen strong bases are most common. Examples (and names) of RO$^{\ominus}$ bases →	
Examples of $R_2N^{\ominus}$ bases →	
Examples of $R_3C^{\ominus}$ bases →	

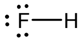
** A topic for next chapter: The -1 formal charge of nitric acid is not "localized" on O, so it is not a strong base!*

Critical Thinking Questions

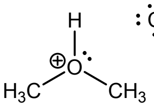
22. (E) For each strong acid in Table 4.3, circle the H that can be donated.

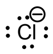
23. (E) Label each of the following as **strong acid, strong base,** or **neither**.

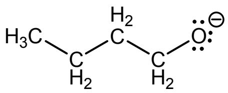


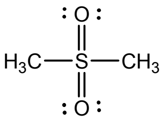


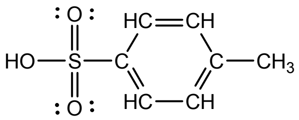
HNO_3











Model 8: Conjugate Acid-Conjugate Base Pairs

Most any molecule can serve as an acid (it simply must have an H), and any molecule with a lone pair can be a base. Most (except those defined above as *strong*) are ***weak* acids** and ***weak* bases**.

General Definitions:

acid = any molecule with an H (e.g., **H—Z**) ← generalized form, where Z can be any atom or group.
Examples of weak acids: H_2O, HOR (alcohols), HF, $^{+}NHR_3$ (ammonium ions), H_2CO_3, many others.

base = any molecule with a lone pair (e.g., **:Z** or **:Z** $^{\ominus}$) ← weak base can be neutral or negative
Examples of weak bases: H_2O, HOR (alcohols), NR_3 (amines), $NaHCO_3$, ROR (ethers), many others.

(Later we will add "or any molecule with π electrons" to our definition of a base—don't worry about this for now.)

H—Z and :Z $^{\ominus}$ are a **conjugate acid-conjugate base** pair (as shown below).

$H_3O^{\oplus}$ and H_2O are another **conjugate acid-conjugate base** pair.

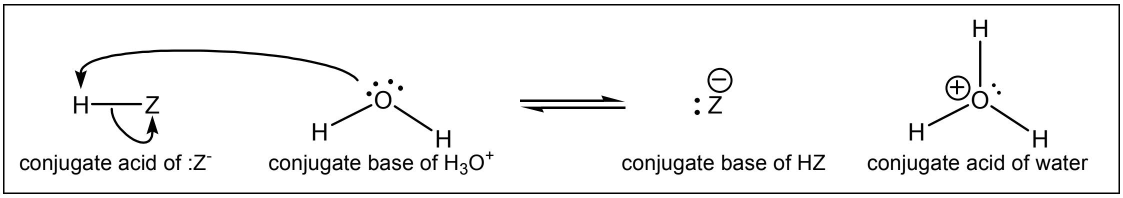


Figure 4.11: Conjugate Acid-Conjugate Base Pairs

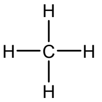
Critical Thinking Questions

24. (E) What is the molecular formula of the conjugate acid of water?

25. Draw the structure of the conjugate base of water. (Note that it does not appear in Figure 4.11).

26. Does Cl $^{\ominus}$ have a conjugate acid? If so, what is it? … a conjugate base? If so, what is it?

27. Draw the conjugate base of CH_4 (methane).



28. For the previous four questions, label each molecule that appears in the question or your answer as **strong acid**, **strong base**, **weak acid**, or **weak base**.

Model 9: Energy Diagrams

Chemists chart the total energy of a chemical reaction vs. time using a graph called an **energy diagram**.

Think of an **energy diagram** as a side-view (cross-section) of a mountainous landscape. By analogy to gravitational potential energy (an object at high altitude has farther to fall), the tops of the peaks are the high **Potential Energy (P.E.)** points of the reaction. The valleys are the low P.E. points.

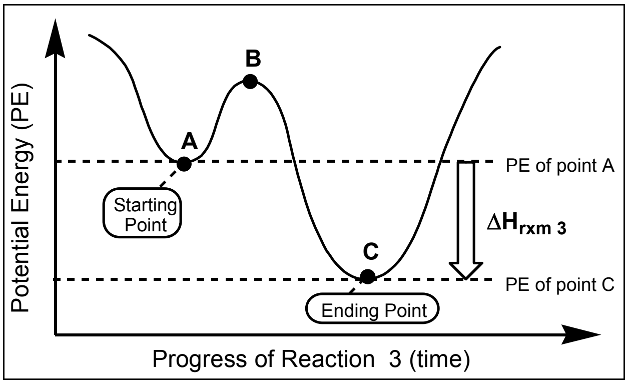


Figure 4.12: Overall Favorable (downhill) Reaction

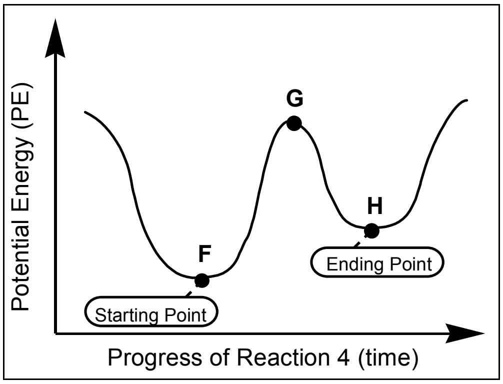


Figure 4.13: Overall Unfavorable (uphill) Reaction.

Memorization Task 4.2: Memorize the following energy diagram conventions...

- a P.E. change* (*ΔH*) from **high to low** is considered "**downhill**" or "**negative (–)**" or "**exothermic**"
- a P.E. change* (*ΔH*) from **low to high** is considered "**uphill**" or "**positive (+)**" or "**endothermic**"

**Organic chemists often use change in heat (ΔH) as an estimate for the change in total* P.E. *for a reaction (ΔG).*

- **Making a bond is downhill, negative (–), exothermic →** energy is released by molecule
- Breaking a bond is uphill, positive (+), endothermic → energy must be added to molecule

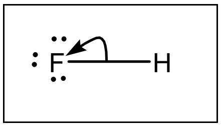
Critical Thinking Questions

29. (E) Is Reaction 3, taken as a whole from Point A to Point C, **endothermic** or **exothermic**? What about Reaction 4? [Label both Figure 4.12 and Figure 4.13 with one of these two terms.]

30. According to the conventions above, what is the sign (+ or –) of the P.E. change (*ΔH*) for Rxn 3?

31. Draw an arrow on Figure 4.13 representing $\Delta H_{rxn\ 4}$. (*Hint*: study the $\Delta H_{rxn\ 3}$ arrow in Figure 4.12)

32. Consider the process shown at right using a curved arrow:



a. Draw a + or – above this curved arrow indicating the sign of the energy change associated with this process, and briefly explain your reasoning.

b. Is breaking the H—F bond uphill or downhill in energy? …favorable or unfavorable?

c. Is this arrow more likely associated with Fig. 4.12 or Fig. 4.13?

33. Add a + or – above each curved arrow in Figure 4.11 to show the sign of the energy change.

PART C: ACID-BASE REACTIONS AND pK_a

(What can a pK_a value tell you about a molecule and its conjugate base?)

Model 10: pK_a as an Estimate of H—Z Bond Strength

Each acid (H—Z) has an experimentally determined pK_a value. **pK_a** is a measure of the energy difference between the conjugate acid (H—Z) and the conjugate base ($Z^{\ominus}$) *in the solvent, water*. This means pK_a is an estimate of…

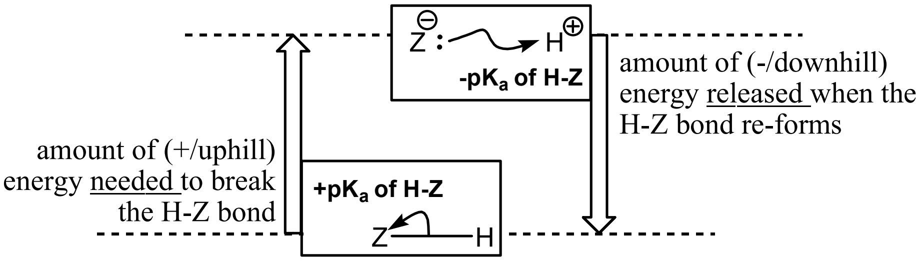
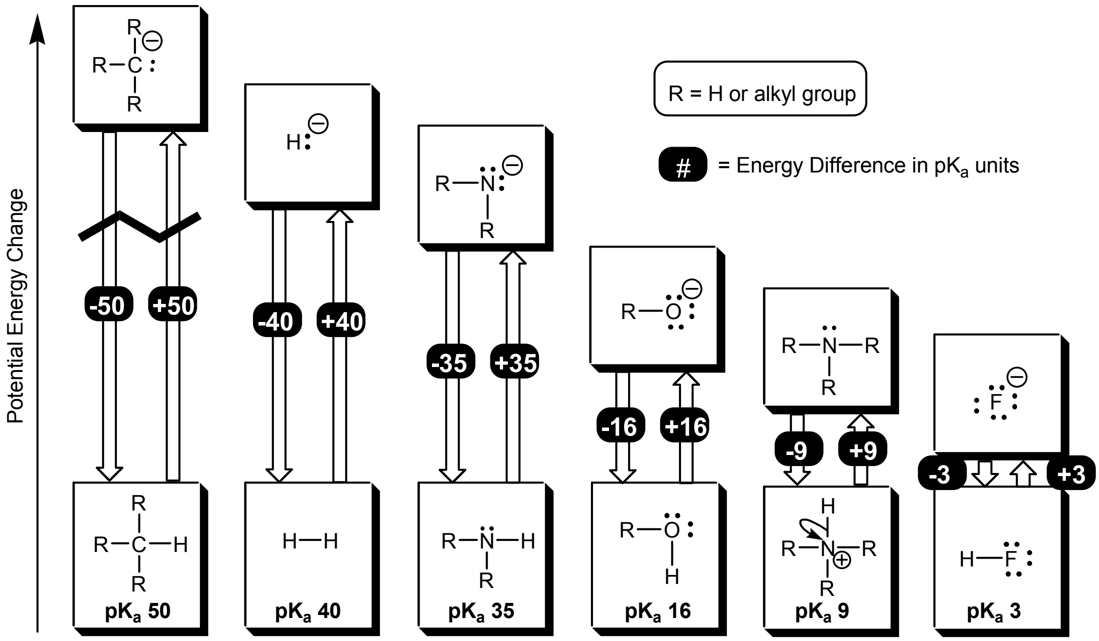

Z:
H
-pKa of H-Z
amount of (-/downhill) energy released when the H-Z bond re-forms
amount of (+/uphill) energy needed to break the H-Z bond
+pKa of H-Z
Z
H

Table 4.5: Energy Differences Between Conjugate Acid-Base Pairs (in pK_a units)



Critical Thinking Questions

34. (E) In Table 4.5, review which structure is the **conjugate acid** and which structure is the **conjugate base** in each column.

35. (E) How much energy is released when the lone pair on $H_2N^{\ominus}$ makes a bond to an $H^{\oplus}$? (Give the value and sign of the energy change in pK_a units.)

36. A student answers "-9" to the previous question. What mistake did this student make?

37. Find the *one* curved arrow on Table 4.5. What is the energy change associated with this arrow?

38. Which will give up (donate) an $H^{\oplus}$ more easily, a conjugate acid with a **high p*K*** —

39. Is your answer to the previous question consistent with the fact that the six strong acids we will study in this course have pK_a values close to zero? Explain.

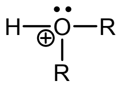
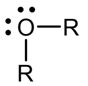
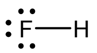
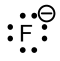
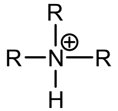
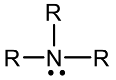
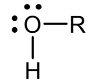
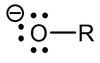
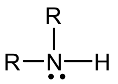
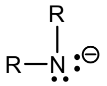
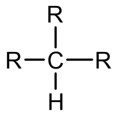
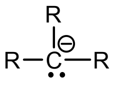
Memorization Task 4.3: Assume all six strong acids (*see* Table 4.3) have a pK_a ≈ 0.

Strong acids actually have negative pK_a values. This is the result of solvent effects that we will not discuss at this point. For now, it simplifies things to make the "strong acid zero pK_a assumption."

40. (E) According to the "strong acid zero pK_a assumption" described above, approximately how much energy is required to break the H—Z bond of a strong acid?

41. Is your answer to the previous question consistent with the fact that strong acids give up an $H^{\oplus}$ very, very easily? Explain why or why not.

Table 4.6: pK_a Table

Conj. Acid	approximate pK_a	Conj. Base
	~ 0	
	3	
	9	
	16	
	35	
H—H	40	:H⊖
	50	

Definition of a Strong Base from Table 4.4: Molecule with a [lone pair] and [-1 charge] *localized** on H, C, N, or O.

42. (E) Identify each "**strong acid**" and "**strong base**" on Table 4.6.

43. A strong base releases a [**large** or **small**] amount of energy when it makes a bond to $H^{\oplus}$. (*circle one*)

44. Label the ***weakest* acid** (that is an acid) and ***weakest* base** (that is a base) on Table 4.6.

45. Choose the letter (a-e) that best completes the "new" definition of a strong base so that it is consistent with our "old" definition of a strong base above.

New Definition of a Strong Base:
Strong Base = molecule whose conjugate acid has a pK_a

a. ~ 0
b. > 5
c. < 5
d. >14
e. <14

Model 11: Using pK_a to Estimate ΔH_{rxn} (heat of reaction)

You can use pK_a values to calculate the energy change (ΔH in pK_a units) for an acid-base reaction, e.g.:

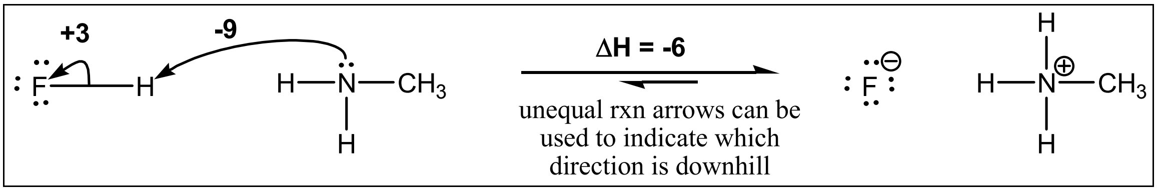

+3
-9
ΔH = -6
unequal rxn arrows can be used to indicate which direction is downhill

Figure 4.14: Use of pK_a to Calculate ΔH for the Reaction of HF with CH_3NH_2

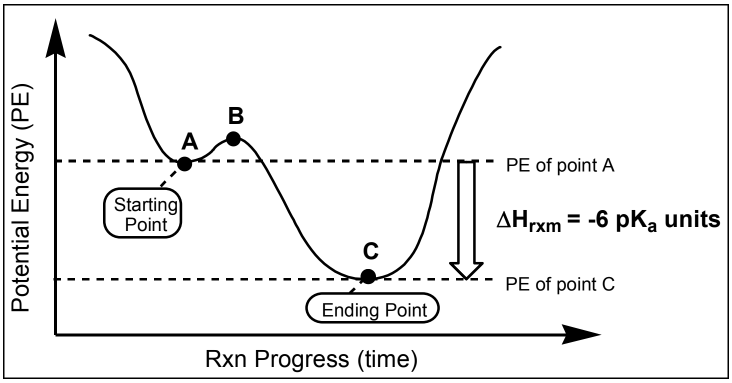


Figure 4.15: Energy Diagram of the Reaction of HF with CH_3NH_2

Critical Thinking Questions

46. (E) Estimate the energy difference (to the closest pK_a unit) between Point A and Point B on Figure 4.15. This value is called the **activation energy** (***E_{act}***), the energy required to start a reaction.

   a. Add a vertical arrow to Figure 4.15 indicating the size and direction of E_{act} for this reaction.

   b. Most students assume that E_{act} should be +3 for this reaction. It turns out that pK_a values are useful for calculating ΔH, but not useful for calculating E_{act}. **Assume $E_{act} \approx$ +1 pK_a unit for all acid-base reactions.** Is this assumption consistent with your answers above?

47. For NH_3 (ammonia) and H_2O (water)…

   a. Use curved arrows to show the most likely acid-base reaction, and draw the resulting products. *(Hint: First decide which is the stronger acid, and which is the stronger base.)*

   b. Mark each curved arrow with a positive (bond-breaking) or negative (bond-forming) number indicating the energy change associated with that arrow (in pK_a units).

   c. Calculate ΔH_{rxn}, and write this number above a set of reaction arrows that indicate which direction is downhill/favorable (in the example, the reaction is downhill to the right).

   d. Sketch an energy diagram for the reaction.

   e. Is your energy diagram consistent with the fact that, in this case, the most likely acid-base reaction is endothermic?

Model 12: Which H is most acidic?

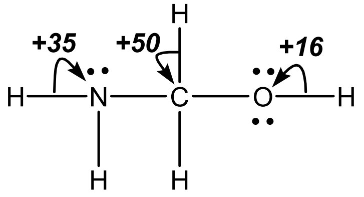
The **most acidic H** on a molecule is the H that **requires the least energy to remove.**

The pK_a value next to a molecule on a **pK_a table** (e.g., Table 4.5) refers to its **most acidic H**.

If there are multiple equivalent "most acidic hydrogens" the pK_a tells you the energy required to remove the FIRST "most acidic hydrogen." (Subsequent H's are much harder to remove).

Critical Thinking Questions

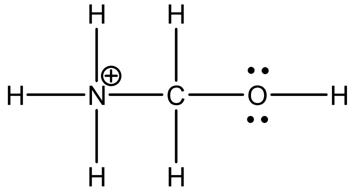
48. (E) Explain where the numbers +35, +50, and +16 (assigned to the curved arrows) came from.



a. (E) Circle the H on this molecule that requires the least energy to remove (the most acidic hydrogen).

b. (E) Is your answer to the previous question consistent with the fact that, on a table of pK_a values, this molecule would be assigned a pK_a very close to 16?

49. Circle the most acidic H on the following molecule. If there is a tie for most acidic, circle all H's that tie for most acidic.



a. Estimate the amount of energy required to remove the most acidic H.

b. What pK_a value would you expect to find next to this molecule on a pK_a table?

Model 13: The Inductive Effect

Polarization caused by an electronegative atom (e.g., F) can induce minor polarization in neighboring bonds.

This is called the **inductive effect**.

Imagine a brick thrown into a still pond. The wave is intense at the impact site, but small even a short distance away.

Warning: The inductive effect is weak. It cannot change that an H on a positive atom is more acidic than an H on a neutral atom or that an H on N or O is more acidic than an H on C.

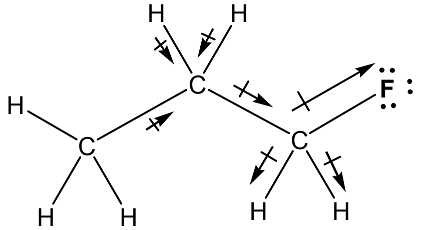
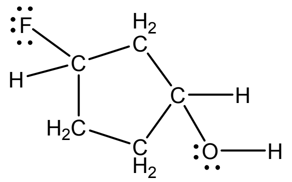


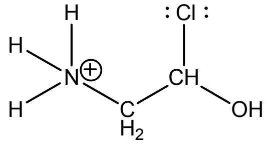
Figure 4.16: Dipole Moments

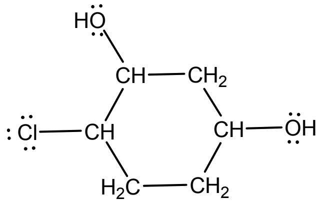
Critical Thinking Questions

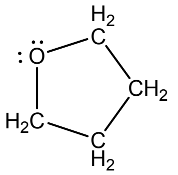
50. Circle the most acidic H/H's on the structure in Figure 4.16, and explain your reasoning.
51. Construct an explanation for why no dipole moment arrows are shown on the C—H bond on the left of the molecule in Figure 4.16.

52. Circle the most acidic H on each structure and explain your reasoning. (If there is a tie, circle more than one H).









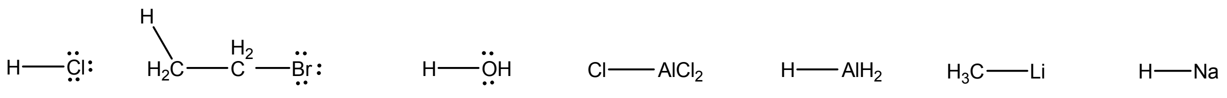
53. What is the purpose of the previous question? (What misconception is it designed to dispel?)

Exercises for Part A

1. When liquid water freezes into ice, the water molecules form up into an orderly repeating pattern and it ceases to flow.
   a. (E) According to Model 1 and your firsthand experiences, which takes up less space: H_2O in the orderly repeating pattern found in ice or H_2O in the fluid arrangement of molecules found in liquid water?
   b. Is your answer to the previous question consistent with the fact that ice floats in water? Explain.

2. Energy must be added to liquid water in order to make it boil (or evaporate) into gaseous water. In what ways does the energy that has been added change the system?

3. For each of the following molecules…



   a. Calculate the EN difference for each “polar” bond. (Assume C—C and C—H bonds are nonpolar.)
   b. Draw a dipole moment arrow for each polar bond.
   c. Add δ+ and δ – to atoms you expect to have a lack or excess of electron density.
   d. Sketch the electron cloud for the molecule so as to indicate areas of high and low electron density.

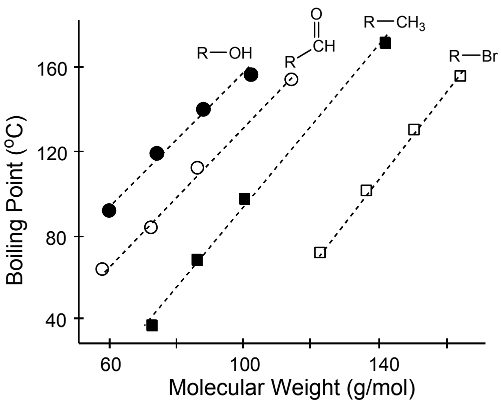
4. Carbon tetrachloride (CCl_4, boiling point = 77°C) is a very potent ozone depleter. An unscrupulous technician decides to dispose of 100 mL (approximately 1 mole) of CCl_4 by boiling it off into the atmosphere. Estimate the percentage of C-Cl bonds in the original ~6×10^{23} molecules of CCl_4 that are broken during this boiling process.

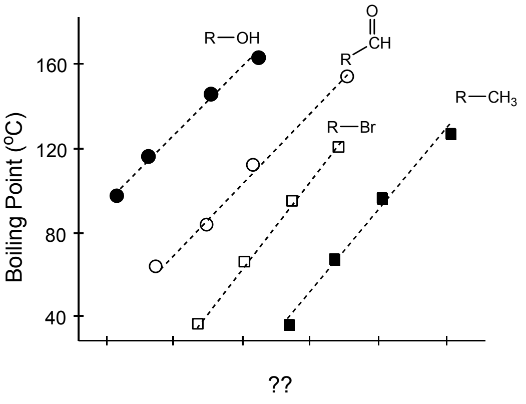
5. Compare the strength of the following two effects to each other, and for each effect, draw the structure of a molecule whose boiling point is primarily determined by that effect.
   - dipole-dipole attraction
   - induced dipole-induced dipole attraction (London or dispersion forces)

Note: Attractive forces called dipole-induced dipole forces occur when a fixed dipole interacts with a nonpolar molecule.

6. *"It seems to me that a molecule without a dipole moment should be a gas at any temperature."* What information is the author of this erroneous statement missing?

7. A student decides to graph bp vs. molecular weight. This graph is shown below, on the left.
   a. What **boiling point** trends are highlighted by this graph?
   b. The alkyl bromide (R-Br) line seems out of place to this student. She feels the alkane line (R-CH_3) should be farthest to the right. Construct an explanation for why she thinks this.
   c. She brings her graph to her professor. The professor suggests that she make a new graph with a different property plotted on the x axis. When the student does this, the graph comes out as she expected. What molecular property is plotted along the x axis of this new graph? (Shown below, right.)





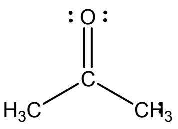
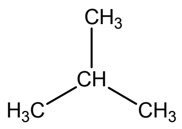
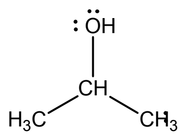
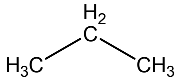
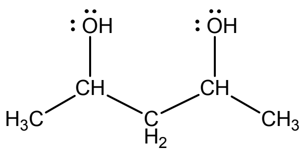
8. Learn the rules for naming alkanes. (**Alkane** = a molecule made up exclusively of C and H atoms connected via single bonds.) These rules are the first topic in Nomenclature Worksheet 1.

9. Read the assigned sections in your text, and do the assigned problems.

Exercises for Part B

10. Propanal (bp 48°C) and propanol (bp 97°C), both found on Table 4.2, have very similar surface areas and dipole moments. Construct an explanation for the large difference in boiling points between the two.

11. Rank the following molecules from lowest to highest boiling point.

Summary of key intermolecular attractive forces:

[strongest] **hydrogen bond**: polar molecules with [H on N, O, or X] and [lone pair on N, O, or F]

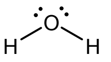
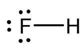
[weak] **dipole-dipole forces**: polar molecules

[weaker] **dipole-*induced* dipole**: when polar molecules or surfaces interact with nonpolar molecules

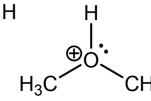
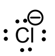
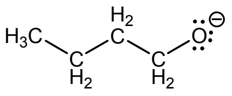
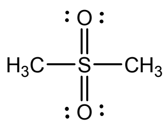
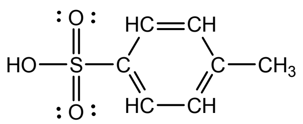
[weakest] ***induced* dipole-*induced* dipole**: most important force for nonpolar molecules

12. Draw the conjugate base of each strong acid shown in Table 4.3 and the conjugate acid of each strong base shown in Table 4.4.

13. For each molecule below, draw the conjugate acid or conjugate base or both if the molecule has both a conjugate acid and a conjugate base (e.g., water).

HNO_3

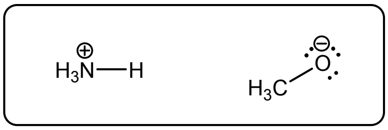
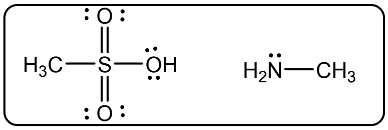
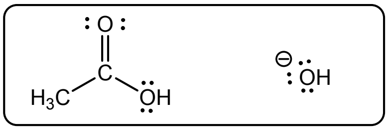






14. For each structure you drew in the answer to the previous question, classify it as a strong acid, strong base, weak acid, or weak base.

15. Mark each of the following statements True or False:
    a. The conjugate base of a strong acid is always a weak base.
    b. The conjugate acid of a strong base is always a weak acid.
    c. The stronger the acid, the weaker its conjugate base, and vice versa.

16. Organic chemistry is a bit like cooking. Later in this course we will study "recipes" for preparing new molecules. A common instruction in such recipes is "add a **strong acid**" or "add a **strong base**" (rarely are they added at the same time since a violent reaction ensues). You will see these terms frequently from now on, and are expected to be able to recognize them or draw their structures from memory. Memorize them before next class.

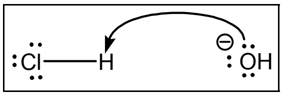
17. Use curved arrows to show an acid-base reaction between each of the following pairs of reactants. In each case, the base is drawn on the right.

18. For each curved arrow that you drew in the previous question, write a sentence that translates into words what that arrow is saying.

19. Are endothermic reactions favorable or unfavorable? … uphill or downhill?

20. Is the arrow at right more likely associated with an energy change from the energy diagram in Figure 4.12 or Figure 4.13?



21. Is bond formation endothermic or exothermic? Write a + or – sign above the arrow in the previous question to represent the sign of the energy change associated with the arrow.

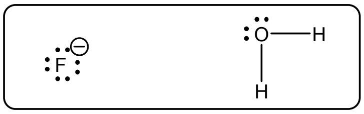
22. Read the assigned sections in your text, and do the assigned problems.

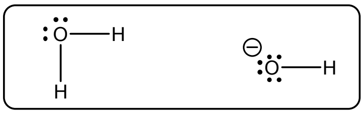
Exercises for Part C

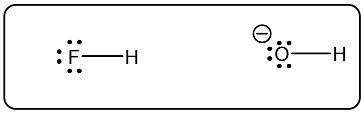
23. Summarize the relationship between pK_a and acid strength by completing the following sentences:
    a. The higher the p*Ka* of an acid, the **stronger** or **weaker** the acid.
    b. The lower the p*Ka* of an acid, the **stronger** or **weaker** the acid.

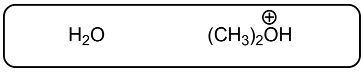
24. Summarize the relationship between pK_a and base strength by completing the following sentences:
    a. For a given base, the higher the pK_a of its conjugate acid, the **stronger** or **weaker** the base.
    b. For a given base, the lower the pK_a of its conjugate acid, the **stronger** or **weaker** the base.

25. Perform a) through d) from CTQ 47, and calculate K_{eq} for each pair of reactants.

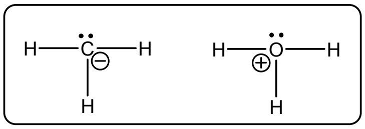


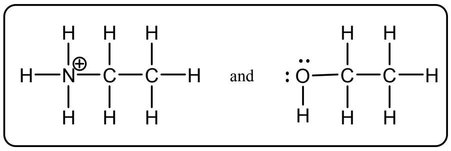




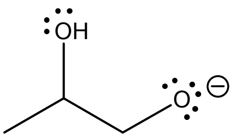


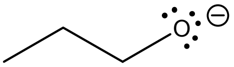
H_2O $(CH_3)_2\overset{\oplus}{O}H$

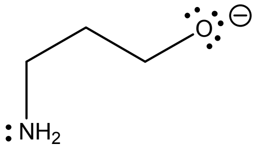


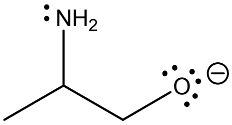


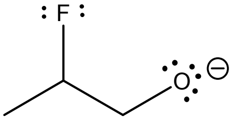
26. Consider the following bases:

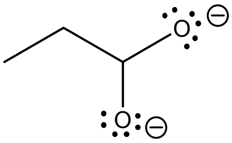








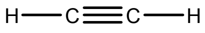




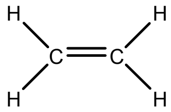
a. For each base above, circle the atom/atoms with the highest PE (will release the most P.E. when a lone pair on this atom combines with an H^+)

b. Rank the bases 1 (highest P.E./strongest base) to 7 (lowest PE/weakest base), and explain your reasoning.

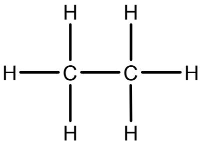
27. Consider the pK_a's listed below:



pK_a 25



pK_a 45



pK_a 50

a. Draw each conjugate base, and using the pK_a data, rank the conjugate bases from strongest base/highest P.E. to weakest base/lowest P.E.

b. For each conjugate base, indicate the type of orbital in which the lone pair of electrons resides. (*Hint*: What is the hybridization state of the atom holding the lone pair?)

c. Indicate the percent *s* character ("red clay") of each orbital holding a lone pair.

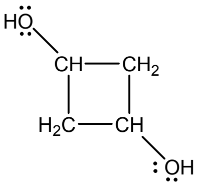
d. Which is lower in PE, an *s* orbital or a *p* orbital?

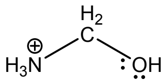
e. Construct an explanation for the pattern in the pK_a data above.

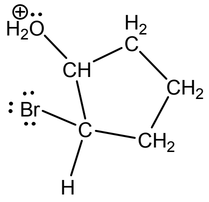
28. The following are equivalent ways of asking about the acidity of an H atom:
    - What is the most acidic H on the molecule?
    - Which H is associated with the published pK_a value?
    - Which H on the molecule is easiest to remove?
    - Which H on the molecule takes the least energy to remove?
    - Which bond to an H is most polarized?
    - For which H atom is removal least uphill in energy?
    - Which bond to an H atom, when broken, results in the lowest PE conjugate base?

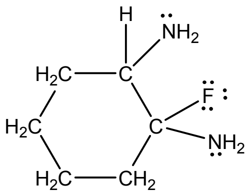
We will often find the last of these questions is easiest to answer. To do this, **find all the different H atoms on the molecule, and draw all possible conjugate bases**. Only the lowest-energy one is the "real" conjugate base. Identify this structure, and you have found the most acidic H.

Use this strategy to find the most acidic H on each of the following molecules. Note: Each structure has at least three different kinds of H's, so draw at least three unique conjugate bases for each.









29. The equilibrium constant for the reaction from CTQ 47 is given below. [Square brackets] represent the concentration of that ion or molecule in moles/liter at equilibrium.

$$\boxed{K_{eq} = \frac{[^{+}NH_4] \times [HO^{-}]}{[NH_3] \times [H_2O]} = 10^{-7}}$$

a. Is K_{eq} for this reaction a very large number or a very small number? For this reaction at equilibrium, will there be more **reactants** or **products**?

b. Chemical reactions, like water in a riverbed, tend to go downhill. Is your answer in part a consistent with the energy diagram you drew for this reaction in CTQ 47?

c. Which of the following best describes the mathematical relationship between ΔH (in pK_a units) and K_{eq}?

$$K_{eq} = \Delta H \qquad K_{eq} = \Delta H^{10} \qquad K_{eq} = 10^{\Delta H} \qquad K_{eq} = 10^{-\Delta H}$$

30. Read the assigned sections in your text and do the assigned problems.

The Big Picture

How does this ChemActivity fit with previous and upcoming activities? The Big Picture section is designed to help you answer this question.

The title of the activity: Polar Bonds, Polar Reactions, foreshadows the fact that almost all reactions we will study in this course are **polar reactions**. That is, they involve the breaking of bonds to yield partial (or full) + and – charges. Naturally, a bond that is already polarized (e.g., H—Cl) is primed to participate in a polar reaction. Acid–base reactions are just the first example, but you will see that all polar reactions contain elements of acid-base chemistry.

Blindly memorizing everything in this workbook is not an effective (or enjoyable) strategy, but it is critical that you memorize certain key bits of information. Before next class, go back through this ChemActivity and transcribe all information in the **Memorization Tasks** sections onto note cards (e.g., key pK_a values). It is best to put the information to be memorized on the back and a hint on the front (e.g., "16" on back; "pK_a of HOR" on front). Carry these note cards in your back pocket and flip through them whenever you have a spare minute. The key to memorization is repetition.

The approximate pK_a values and the energy conventions laid out in this activity are the keys to understanding acid-base reactions and all other polar reactions in this course. A moderate time investment at this point will save you vast amounts of frustration farther down the line. These memorized bits of information will serve as a crutch while you develop your deeper conceptual understanding of organic chemistry.

As an aside, some students wonder why we memorize approximate pK_a values (e.g., 16 for water, though the actual number is 15.7; zero for H_3O^+, though the actual number is -1.7, etc.). The answer is that our reason for memorizing pK_a values is to know the *relative* acidities and basicities of the molecules we will encounter in this course. In other words, it is important to know that NH_3 is a stronger base than H_2O, but not necessary to know exactly how much stronger it is. If you have memorized the pK_a's of the conjugate acids as 9 and 0, respectively, this will tell you that NH_3 is a much stronger base than H_2O. And though our approximations introduce some error in our calculations of ΔH from pK_a differences, it is well worth the trade-off in terms of the ease of memorizing round numbers.

Common Points of Confusion:

- An H attached to a C atom cannot participate in hydrogen bonding.
- Many students think of acid-base reactions as all or nothing. They erroneously assume that if the reaction is favorable (e.g., NH_3 + HF, which is downhill by 12 pK_a units of energy) then all NH_3 and HF molecules will be consumed during the reaction. This is not the case with this reaction (and, in fact, no reaction goes 100.000…etc. percent to completion. There is always an **equilibrium** point where the concentration of products causes the reaction to stop. At this point there are always some reactant molecules still around. The more the energy difference between reactants and products (the more downhill the reaction), the fewer reactant molecules remaining when the equilibrium point is reached.
- You may have used pK_b values in a previous course, but they are not commonly used by organic chemists since the pK_a of an acid tells you both its acidity and the basicity of its **conjugate base**. If you want to know the strength of a base, instead of looking for a pK_b, find the pK_a of its conjugate acid. The higher the pK_a of the conjugate acid, the stronger the basicity of the **conjugate base**.

- H—O—R (water or an alcohol) **can act as a weak acid or a weak base**. But in each case **different p*K*$_a$ values apply**. When acting as an acid you say that it takes +16 pK_a units of energy to break the H—O bond. When it acts as a base you say that about -0 pK_a units of energy are released when the lone pair on oxygen makes a bond to H^+ to form H_3O^+.
- The exact same situation applies to amines (HNR_2). When acting as an acid you say that it takes +35 pK_a units of energy to break the H—N bond. When it acts as a base you say that -9 pK_a units of energy are released when the lone pair on nitrogen makes a bond to H^+ to form $H_2NR_2^+$
- Students love the **inductive effect** and so tend to overestimate its power. Do not assume that an H near a halogen is acidic. Usually it is only slightly more acidic than H's farther away from that halogen. In searching for the most acidic H, be sure to first consider formal charges and atom electronegativities (an H attached to an N or O is much more acidic than an H attached to a C). If neither of these gives you a clear answer, it may be that inductive effects serve as a tiebreaker, making an H near an electronegative element slightly more acidic than one farther away.
- Our treatment of energy differs slightly from the key energy formulas found in most general chemistry textbooks:

  $$\Delta G^o = -RT \ln K_{eq} \qquad \text{and} \qquad \Delta G^o = \Delta H^o - T(\Delta S^o)$$

  The following assumption and proof may help some of you reconcile our treatment of energy, **ΔH** and pK_a, with what you have learned in the past.

  Assumption: $\Delta S \approx 0$ *for most organic reactions, therefore* $\Delta G^o \approx \Delta H^o$

  Proof that p*K*$_a$ is a measure of energy proportional to *ΔG*:

  $\mathbf{p}K_a = -\log K_a$, and under standard conditions $K_a \propto K_{eq}$ ($\propto$ = "proportional to")

  $\Delta G^o = -RT \ln K_{eq}$, since $(\log x) \propto (\ln x)$ it follows that $pK_a \propto \Delta G^o$

  ΔG^o is a measure of energy, therefore **p*K*$_a$ is a measure of energy**.

ChemActivity 5: Resonance

PART A: DRAWING RESONANCE STRUCTURES

(Why is baking soda [$NaHCO_3$] a *weak* base even though it has an O with a -1 formal charge?)

Model 1: +1 Counterions

We have encountered many -1 anions in this course: $HO^{\ominus}$, $Cl^{\ominus}$, $(CH_3)_2N^{\ominus}$, $HCO_3^{\ominus}$, etc.

If you go to the stockroom you will not find a bottle of "$HO^{\ominus}$" (hydroxide) on the shelf because every anion must exist in close proximity to a **counterion,** an ion that balances out the charge.

In this book we will generally **assume that positive counterions are inert** and that their only function is to balance the negative charge of the anion.

Also assume that all ions appearing in this book have a counterion, even if one is not specified.

If ions in a sample did not have counterions, electrical charge would build up, and the sample would find a way to "ground" itself. For example: ion flow across a salt bridge in a battery, or lightning—the result of ion imbalance in a cloud.

Critical Thinking Questions

1. Which elements on the periodic table (other than H) are likely to form a +1 cation?

2. You will not find "hydroxide" in the stockroom, but you will find sodium hydroxide (NaOH) and potassium hydroxide (KOH). Lithium hydroxide (LiOH) is expensive and used in spacecraft air filters since hydroxide reacts with carbon dioxide, and lithium is lighter than sodium or potassium. Cesium and francium hydroxides are very expensive and little used. Is this information consistent with your answer to the previous question?

Information: $Li^{\oplus}$, $Na^{\oplus}$, $K^{\oplus}$ (= ions) vs. Li^o, Na^o, K^o (= metals)

The use of a superscript zero after an element (e.g., Li^o) indicates the element is in an uncharged **metallic state** (the zero oxidation state). Li^o, Na^o, and K^o are all highly reactive metals we will occasionally encounter in this course—look for the zero superscript (^{o}).

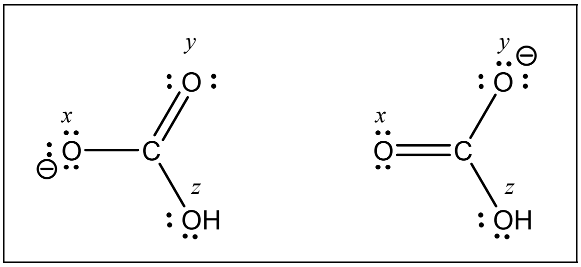
If you don't see the zero superscript (^{o}) after Li, Na, or K, assume it is an inert +1 counterion!

3. For each condensed formula, draw a line-bond structure of the anion, and next to it draw the +1 counterion as a separate ion.

$NaOCH_3$ NaH $Li(CH_2)_3CH_3$ $LiN(CH_3)_2$ $LiAlH_4$

Model 2: Two Lewis Structures for Baking Soda ($NaHCO_3$)

There are two different but equally good ways to draw a legitimate Lewis structure of bicarbonate ion.



Neither structure by itself tells the whole story.

To get the most accurate picture of bicarbonate ion you must **average the two different structures**.

Figure 5.1: Bicarbonate Ion ($HCO_3^{\ominus}$)

To facilitate the following discussion, the three oxygens of bicarbonate were labeled O_x, O_y, and O_z.

Critical Thinking Questions

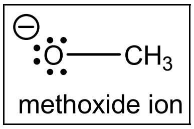
4. A student looks at Model 2 and says she expects the bond between C and O_x to be halfway between a single bond and a double bond (i.e., shorter and stronger than a single bond, but not as short and strong as a double bond) and that the same will be true of the bond between C and O_y.

   Explain how she derived these conclusions from the information in Model 2.

5. Based on the most accurate picture of bicarbonate ion, what is the charge on O_x? … O_y? … O_z? (Note that it may be a fraction.) Briefly explain how you calculated your answers.

6. Organic chemists say that "the -1 charge on bicarbonate ion is 'delocalized' between O_x and O_y." Come up with at least one synonym for the word "delocalized" in the preceding sentence.

7. On which do you expect to have a more intense and concentrated "hot spot" of negative charge: methoxide ion or bicarbonate ion?



8. Recall that one definition of a strong base is: *"A molecule with a -1 formal charge localized on an H, C, N, or O atom."* Construct an explanation for why bicarbonate ion is NOT a strong base.

9. In which location is the $Na^{\oplus}$ counterion of baking soda ($NaHCO_3$) most likely to reside:
   a) next to O_x b) next to O_y or c) halfway between O_x and O_y?
   Briefly explain your reasoning.

Model 3: Resonance Structures

Many ions (e.g., bicarbonate) have charges that are delocalized (shared) among multiple atoms. To obtain an accurate picture, we draw all legitimate Lewis structures of such an ion and average them.

Each of these legitimate Lewis structures is called a **resonance structure (r.s.)**.

Resonate = fit together toward a common purpose or view, e.g., "The candidate's positions really resonate with the voters."

To generate the full set of resonance structures for an ion:

- Draw any one legitimate Lewis structure of the ion
- CAREFULLY follow the **rules for use of curved arrows** to generate the other legitimate Lewis structures of the ion. (Each one will have the charge on a different atom in the ion).

Memorization Task 5.1: Memorize Rules for Using the Three Types of Curved Arrows

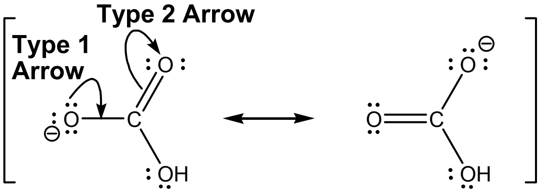
I. For **anions**: Always use Type 1 & 2 in tandem to move a ⊖ charge (may use Type 3 *with* 1 & 2).

II. For **cations**: Use only Type 3 (never 1 or 2) to move a ⊕ charge.

III. You may not break any **sigma** bonds, move any atoms, or change the total number of electrons.

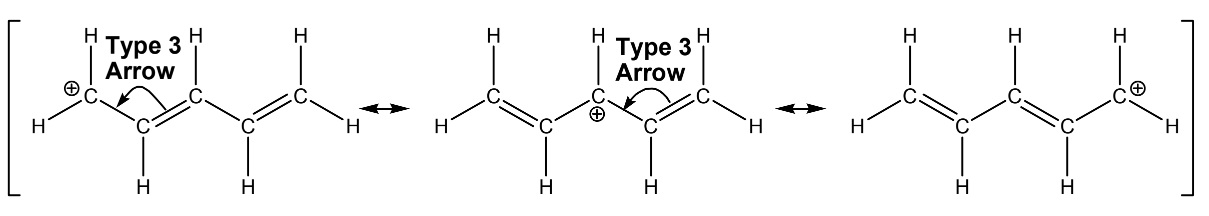
IV. Each C, N, O and X atom must have an octet (exception: carbocations [$R_3C^{\oplus}$] are legal).

Anion Example::



By convention: resonance structures are bracketed together with square brackets and linked with a double-headed arrow.

Cation Example:



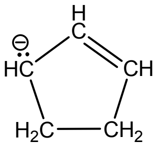
If you cannot legally move any charge (on any resonance structure) to generate a new structure, you are done. There are no more resonance structures in the set for that ion.

Critical Thinking Questions

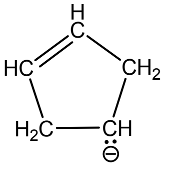
10. (E) Match each of the following descriptions to the correct type of curved arrow (1, 2, or 3):

- A lone pair of electrons becomes a π bond to an adjacent (next-door) atom.
- A pair of electrons in a π bond slides down to become a lone pair on one atom in that bond.
- A pair of electrons in a π bond moves to become a π bond to an adjacent atom.

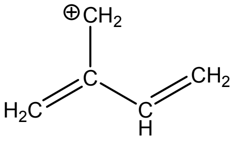
11. Complete the set of resonance structures for the following anion.



12. Construct an explanation for why the Lewis structure below does NOT belong in the set of resonance structures for the ion in the previous question. (What rule was broken in making it?)



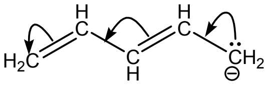
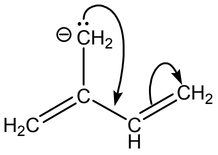
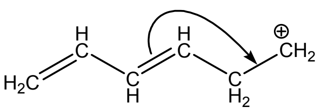
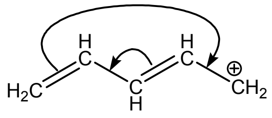
13. Complete the set of resonance structures for the following cation.



14. Is your answer to the previous question consistent with the fact that this cation has a total of **two** resonance structures (***including* the one shown above**)? If not, go back and check your arrows.

15. When drawing resonance structures of an anion, you always start your Type 1 curved arrow at an atom with a -1 formal charge. Describe where you should start your Type 3 arrow when you are trying to draw a resonance structure of a cation.

16. One structure below has a legal set of curved arrows. Each of the other structures has at least one illegal arrow. Cross out all illegal arrows, and briefly explain why each one is illegal.

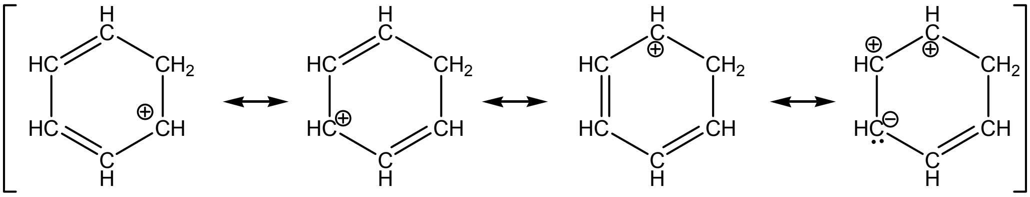
Model 4: Resonance Structures—Important (*vs. Second Order r.s.)*

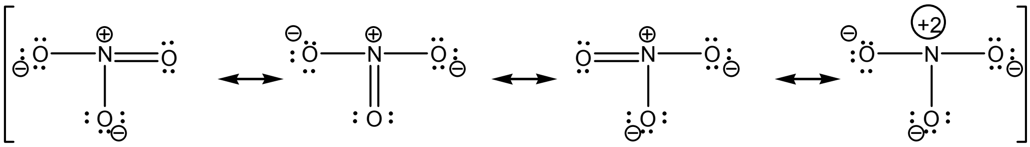
When you are asked to draw all resonance structures of an ion, you should draw only the resonance structures that are very important for understanding the location of charge and electrons on the ion.

These **important** or **first-order resonance structures** are defined as those with the minimum number of +1 and –1 formal charges (and no formal charges larger than +/-1 …e.g., +2, -2, +3, -3, etc.).

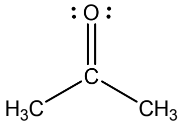
Critical Thinking Questions

17. For each proposed set of resonance structures:
    a. (E) Add curved arrows (starting from left) to show how each successive r.s. was generated.
    b. Cross out any resonance structures that are NOT **important**, and explain your reasoning.



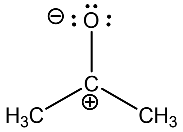


18. Consider the polarization of the C=O bond in the molecule acetone →
    a. (E) Which atom (C or O) is expected to have a greater electron density?
    b. (E) Add a δ+ and δ– to this bond to emphasize its polarization.



Acetone

19. The C=O double bond is called a "**carbonyl bond**." Acetone and other **carbonyl compounds** are introduced in some texts along with this structure →
    a. Is this an **important resonance structure** of acetone? Explain.
    b. Does this structure convey ***any*** useful information about acetone? If so, what?



Information: Second-Order Resonance Structures

Occasionally in this book we will use a resonance structure that is not "**important**" to make argument.

For example, the structure above is often used to emphasize the polarization of the C=O bond.

We will call these useful but much less important resonance structures **second-order resonance structures.** *The important resonance structures are the first-order resonance structures.*

MODEL SET ALERT!! BRING MODEL SETS TO NEXT CLASS.

PART B: RESONANCE STABILIZATION

(What do resonance structures tell us about the relative potential energy of a molecule?)

Model 5: Wavelength and Energy

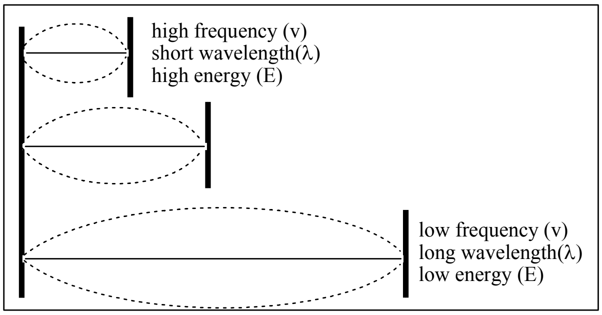


Figure 4.3: Guitar Strings

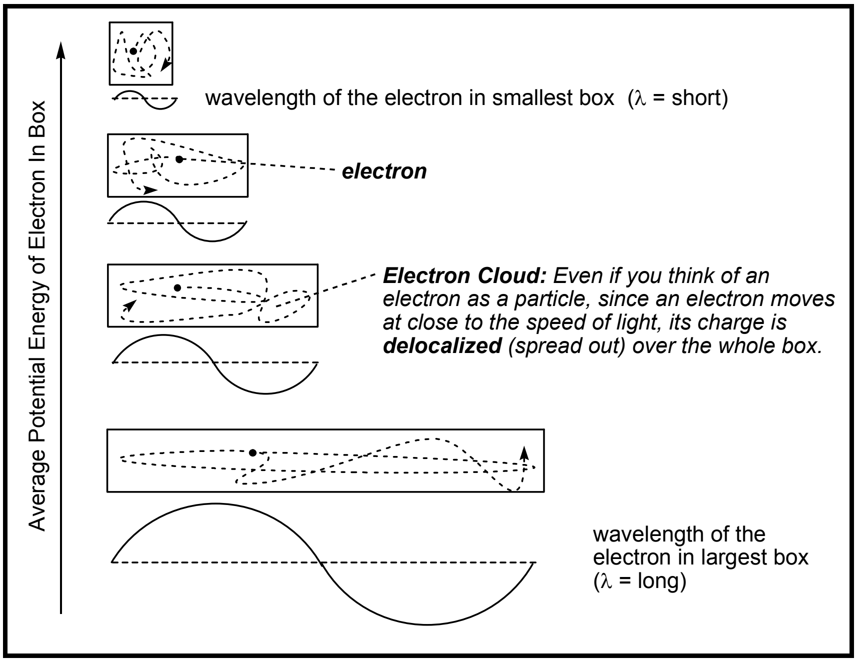
Table 5.1: Properties of Various Kinds of Light

Type	Wavelength	Effect	Energy
X-ray	λ = 0.1 - 10 nm	causes cancer	**very high**
Vacuum UV	λ = 10 - 200 nm	damages tissue	**high**
Ultra-violet (UV)	λ = 200 - 400 nm	causes sun burn	**moderate**
Visible	λ = 400 - 800 nm	energy for plants	**low**
Radio Waves	λ = 0.2 - 20 m (10^9 nm)	relatively safe	**very low**

Imagine an electron confined to a box.

Electrons are so small they behave like light and have a wavelength.

The longer the box, the longer the **wavelength** of an electron in that box.


Average Potential Energy of Electron In Box
wavelength of the electron in smallest box (λ = short)
electron
wavelength of the electron in largest box (λ = long)

***Electron Cloud:** Even if you think of an electron as a particle, since an electron moves at close to the speed of light, its charge is **delocalized** (spread out) over the whole box.*

Figure 5.4: Electrons in Small and Large Boxes (a thought experiment)

Critical Thinking Questions

20. (E) According to Model 5: Light with a short wavelength is **low** or **high** [circle one] in energy.

    a. Light with a long wavelength is **low** or **high** [circle one] in energy.

    b. The electron in which box in Figure 5.4 has the smallest wavelength?

    c. The electron in which box in Figure 5.4 has the lowest energy? Explain your reasoning.

Model 6: More Resonance Structures = Larger "Box"

According to the "Electron in a Box" analogy…

- A charge that is localized on a single atom is confined to a small box.
- A charge that is delocalized over several atoms is in a larger box.

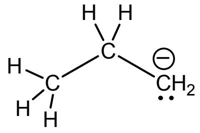
Therefore…

For two similar molecules, the one with more resonance structures will be lower in potential energy. Organic chemists say that molecules with more than one resonance structure are **resonance stabilized.**

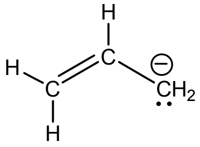
Critical Thinking Questions

21. Draw all missing resonance structures for each of the following anions.

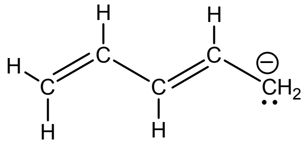
I



II

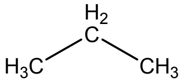


III

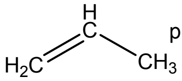


22. Which ion (**I, II** or **III**) [circle one] do you expect to be lowest in potential energy? Explain your reasoning.

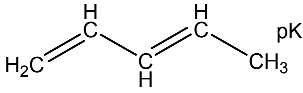
23. Is your answer to the previous question consistent with the following pK$_a$ values? Explain your reasoning.



pK$_a$ 50



pK$_a$ 43



pK$_a$ 35

Model 7: Resonance Structures—Unequal (but still important)

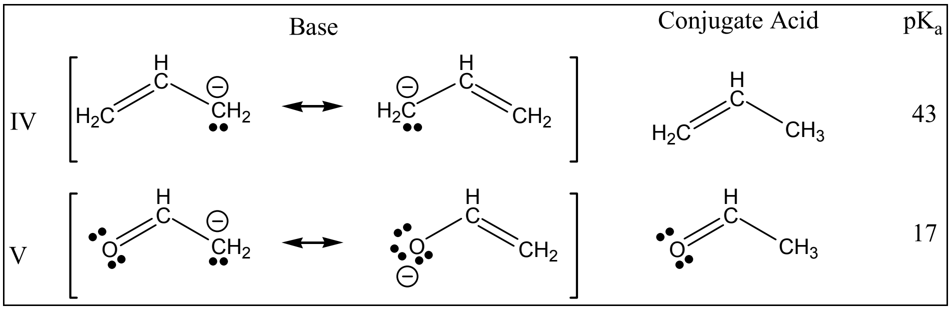


Figure 5.5: pKa Data for Two Ions Demonstrating Resonance Effects

Critical Thinking Questions

24. (E) Based on the pK_a data given in Figure 5.5, write **“weaker base”** next to one base (**IV** or **V**) and stronger base next to the other base.

25. (E) Which base, **IV** or **V** [circle one], is lower in potential energy?

26. One base in Figure 5.5 (**IV** or **V**) has two equivalent resonance structures;
the other base has two resonance structures that are NOT equivalent.

    a. Write **equivalent** below one pair of resonance structures and **NOT equivalent** below the other pair of resonance structures.

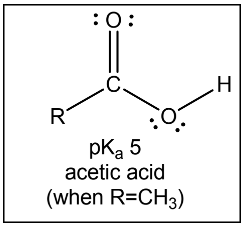
    b. For the pair labeled NOT equivalent, circle the lower potential energy resonance structure, and explain your reasoning.

27. Are your answers above consistent with the fact that, for base V, the resonance structure on the right is called the **more important resonance structure**? Explain your reasoning and this name.

28. Acetic acid, shown below, is a member of a family called **carboxylic acids (RCOOH)**

    a. Draw the conjugate base of acetic acid (called **acetate**), including both important resonance structures.

    b. Acetic acid has a pK_a of 5. Based on pK_a data, rank acetate and the two bases shown in Figure 5.5 from highest to lowest potential energy.



Memorization Task 5.2: Add the following pK_a’s to your list to be memorized

Carboxylic Acid (e.g., acetic acid) p$K_a \approx 5$; Phenol (*see Exercises for Part B*) p$K_a \approx 10$

c. Construct an explanation based on resonance arguments for your potential energy rank order in the previous question. (Note all three bases have two important resonance structures.)

d. Briefly summarize how both the quantity *and quality* of an ion's resonance structures affect its potential energy.

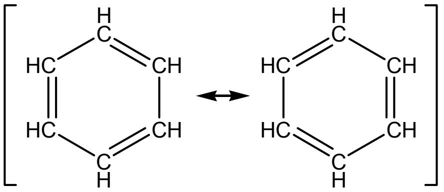
Model 8: Resonance Structures of Neutral Molecules

Occasionally, you will encounter a neutral molecule that has more than one resonance structure.

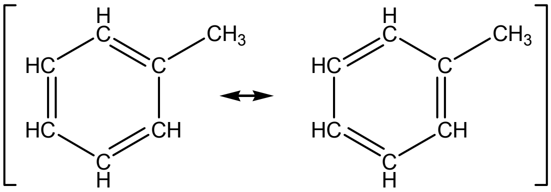
There are two general types:

aromatic molecules = benzene and similar molecules

Use Type 3 Arrows (as described for **cations** in Model 3) for neutral aromatic molecules.



Benzene

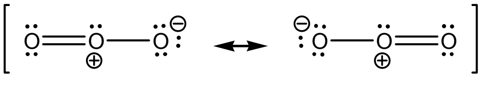


Toluene (also called Methylbenzene)
a common benzene derivative

***Aromatic molecules** are named for the odors of the first members of the family to be discovered. They are frequently encountered, both in nature and the laboratory, and will play a central role in the second half of this book.)*

zwitterions = overall neutral molecules with both ⊕ and ⊖ formal charges (e.g., ozone)

Use Type 1 and 2 curved arrows (as described for **anions** in Model 3) for *zwitterions*



zwitter = German for "hybrid" or "hermaphrodite"

Ozone

Critical Thinking Questions

29. (E) Add curved arrows to the resonance structure of benzene on the left so as to generate the resonance structure of benzene on the right. What type of curved arrow(s) did you use?

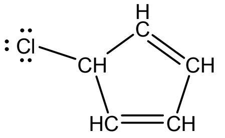
30. Construct an explanation for why benzene and other aromatic molecules are low in potential energy.

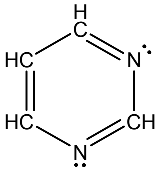
31. (E) Add curved arrows to the resonance structure of ozone on the left so as to generate the resonance structure of ozone on the right. What type of curved arrow(s) did you use?

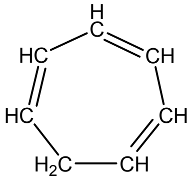
32. Confirm that there is no legitimate Lewis structure of ozone with all zero formal charges.

33. Draw all resonance structures of the molecule nitromethane ($H_3C—NO_2$).

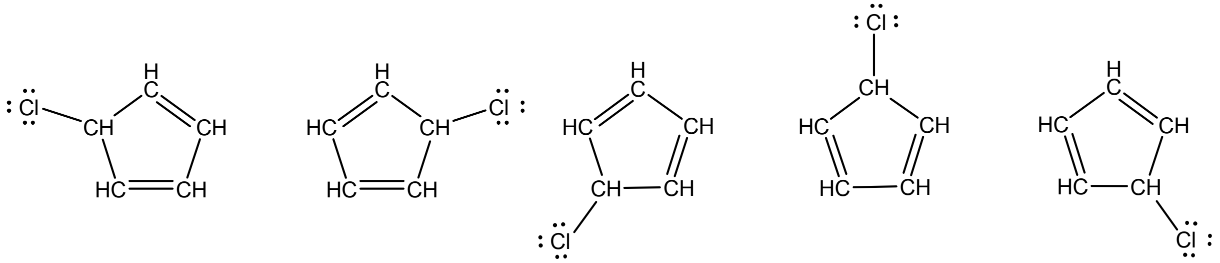
34. Below each molecule, draw all other important resonance structures (if any).

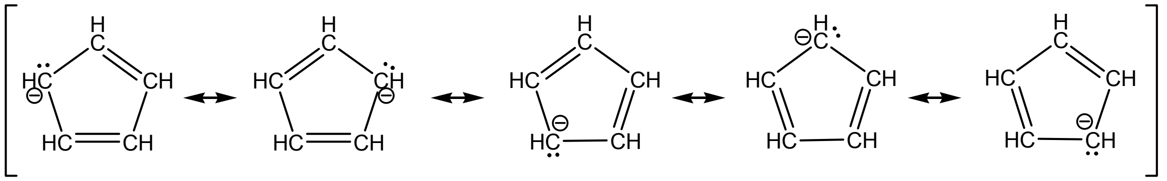






35. The five structures in the top row are considered **identical** representations of the same molecule, whereas the five structures in the bottom row are considered five **different resonance structures**.





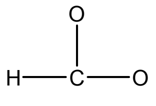
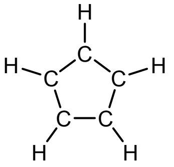
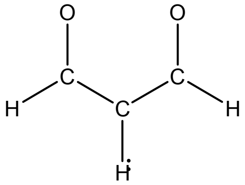
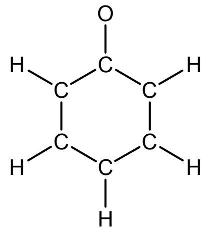
Explain why any one structure is enough to describe the species in the top row, whereas the whole bottom row is needed to describe the species in the bottom row.

36. What is the purpose of the previous question? (What concept or distinction is it designed to help you make? What common misconception is it designed to help dispel?)

Exercises for Part A

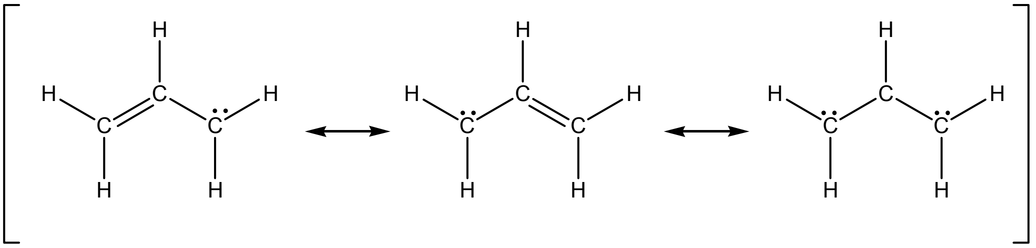
1. Occasionally, we will see an ionic compound that has a -1 counterion. *(Later we will find that – 1 counterions are often more than spectators and take an active role in many reactions.)*
   a. What elements (other than H) on the periodic table are most likely to form a -1 anion?
   b. Draw a Lewis structure for the ionic compound NH_4Cl (*Hint*: One atom is a -1 counterion).

2. The following are -1 anions. Complete each Lewis structure, and draw all important r.s.

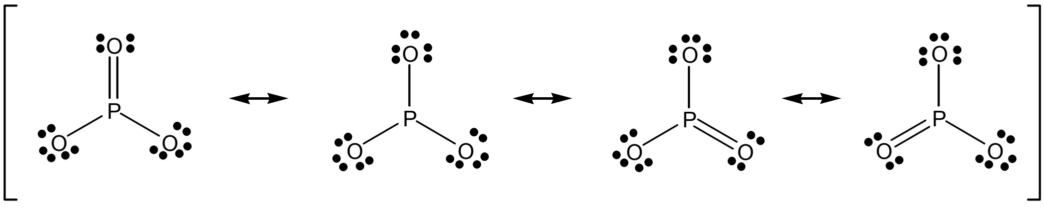





3. For each set, add missing formal charges (all lone pairs shown), and cross out any resonance structures that are NOT important.

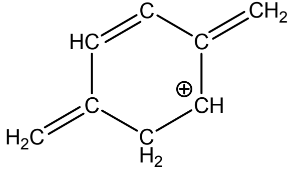
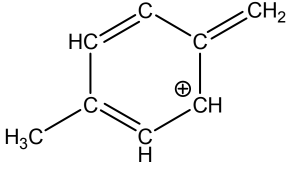
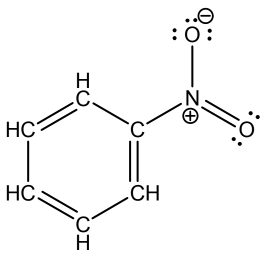
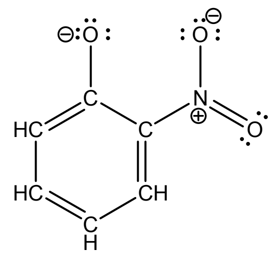
a)



b)

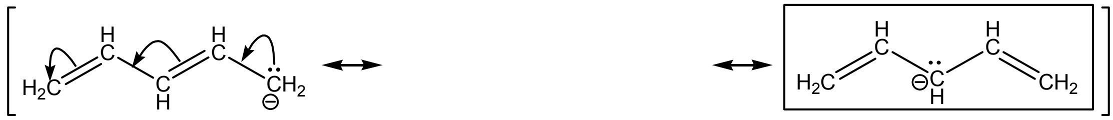


4. Draw all important resonance structures for each ion.

5. Is it possible to draw a resonance structure of nitrate ion ($NO_3^{\ominus}$) that has one formal charge?

6. The electron movements shown below (left) are "legal."

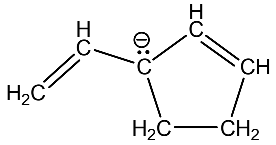


a. Draw the resonance structure that results from these curved arrows.

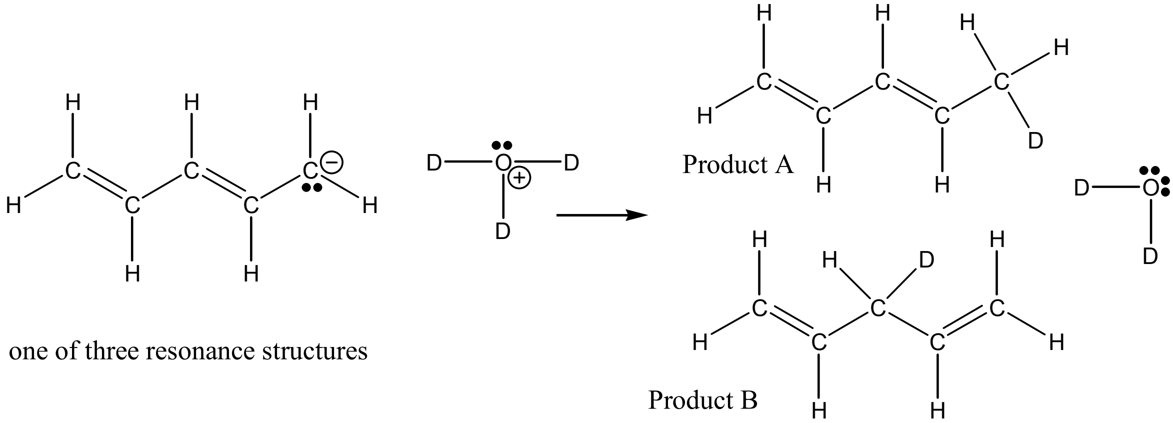
b. A student comments that "Use of a Type 3 arrow on an anion often causes you to 'skip' an important resonance structure." Construct an explanation for why use of a Type 3 arrow caused us to "skip" the resonance structure in the box.

c. Add curved arrows to the resonance structure you drew for part a that show how the resonance structure in the box can be generated from it.

7. Complete the set of resonance structures for the following anion.



8. "D" is not an element on the periodic table. It stands for deuterium. It is an H with an extra neutron. Think of it as an H with a label. We will frequently use deuterium in this course to track a chemical reaction. For example, when the anion below is treated with D_3O^+ (a strong acid almost identical to H_3O^+), two distinct products are observed (Products A and B).



one of three resonance structures

Product A

Product B

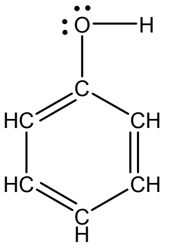
a. Use curved arrows to show a reasonable mechanism for formation of Product B.

b. A student predicts the ratio of A:B in the product mixture will be 2:1. Construct an explanation for this prediction.

9. Read the assigned sections in your text, and do the assigned problems.

Exercises for Part B

10. Phenol (shown below) has a p$K_a \approx 10$.



  a. Based on pK_a data, is phenol a stronger or weaker acid than an ordinary alcohol (e.g., CH_3OH) or water?

  b. Draw the conjugate base of phenol (called phenoxide) including all important resonance structures.

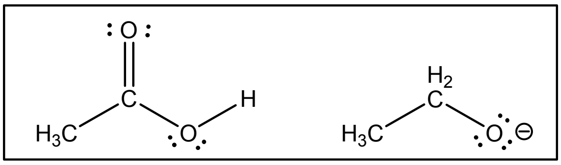
  c. Construct an explanation for why phenol is a stronger acid than an ordinary alcohol. (You may want to consider first why phenoxide is lower in PE than methoxide (RO^-) or hydroxide (HO^-).

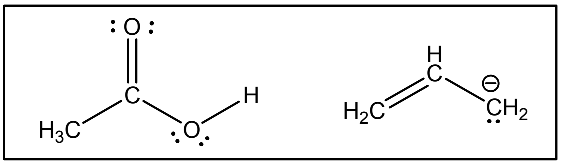
11. Use curved arrows to show the most likely acid-base reaction between phenol and NaOH.

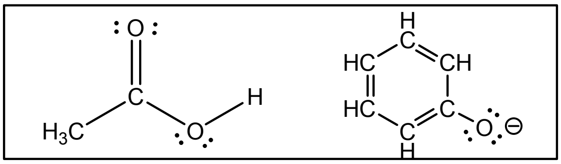
  a. Use pK_a data to mark each curved arrow with a positive or negative energy change in pK_a units.

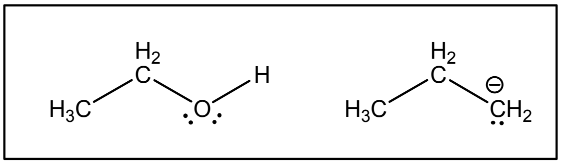
  b. Calculate ΔH for this reaction, and sketch an energy diagram showing ΔH as an arrow on your diagram.

12. Use curved arrows to show the most likely acid base reaction between each boxed pair.









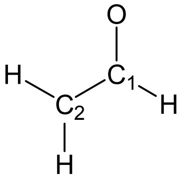
  a. Use the pK_a values in Model 7 and in the previous ChemActivity to mark each curved arrow with a positive or negative energy change in pK_a units.

  b. Calculate ΔH for each reaction, and sketch an energy diagram showing ΔH as an arrow on this diagram.

13. Complete each Lewis structure, draw all important resonance structures, predict a value for the bond angles requested, and explain your reasoning.

  a. Nitrous acid (HNO_2) H—O—N—O ∠HON = ∠ONO =

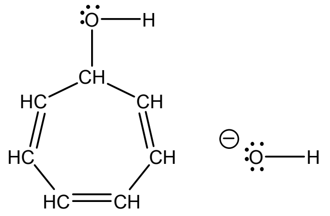
  b. Enolate ion ($C_2H_3O^-$)

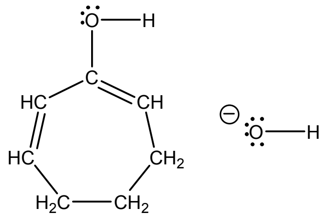


$\angle\ HC_1C_2 =$

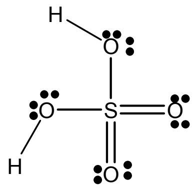
$\angle\ HC_2C_1 =$

14. Use curved arrows to show the most likely acid-base reaction for each pair of reactants below. Draw the resulting products including all important resonance structures. For each reaction, indicate if ΔH_{rxn} is negative, positive, or close to zero, and explain your reasoning.

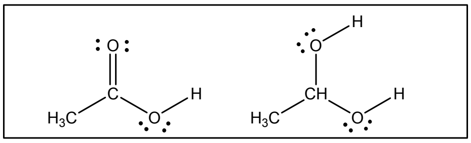
Rxn I


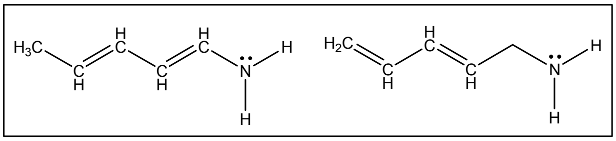
Rxn II


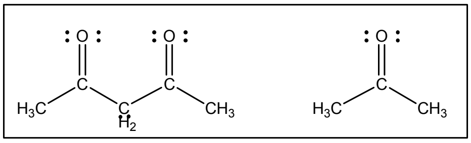
15. Construct an explanation for why sulfuric acid is such a strong acid. (Note that sulfur is in the third row of the periodic table and can have more than eight electrons.)

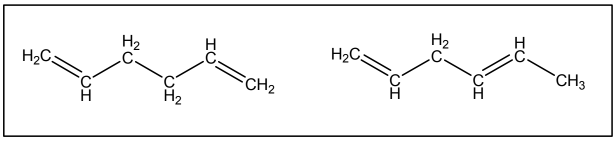


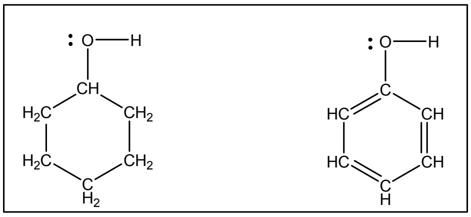
16. For each molecule below, circle the most acidic hydrogens. For each boxed pair, identify the molecule you expect to have a lower pK_a, and explain your reasoning.

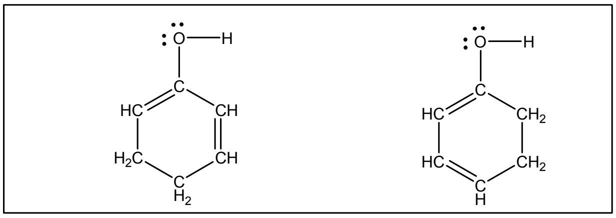




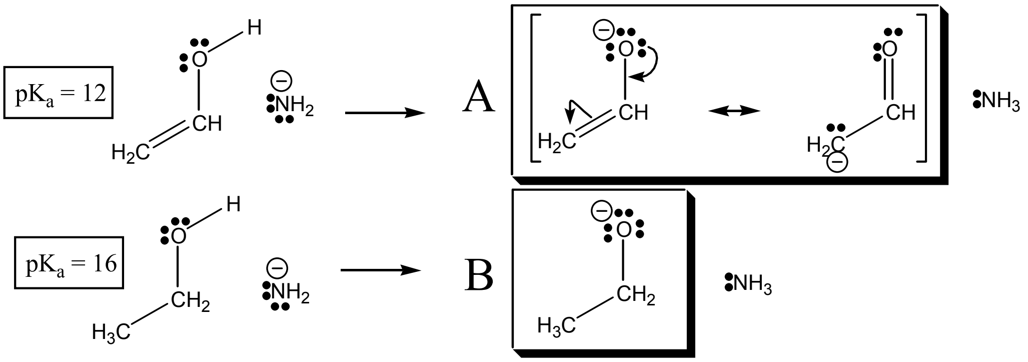








17. Consider the following acid-base reactions:



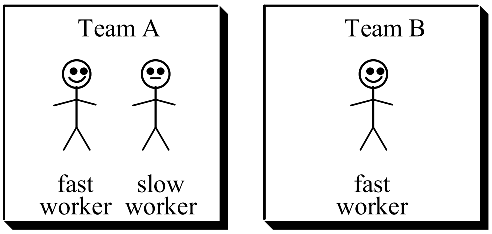
a. Use curved arrows to show each acid base reaction.

b. Based on the pK_a data, which alcohol is a stronger acid?

c. Which conjugate base is lower in potential energy (a weaker base)?

Warning!! Common Sticking Point!! Many students think that conjugate base B should be lower in potential energy because A has an unfavorable negative carbon associated with it. **An additional resonance structure (even if it is not very favorable) can only "help" lower the potential energy of a species. It cannot hurt.** The following analogy helps illustrate this point.

Consider two teams of postal workers racing to postmark 1000 envelopes. Team A consists of a fast worker and a slow worker. Team B consists of a single fast worker. Assume the two fast workers work at the same pace, and the slow worker doesn't bother his fast teammate.



This means Team A will postmark 1000 envelopes before Team B since the slow worker helps some and doesn't hurt at all.

d. Explain how this story relates to the example at the top of the page.

18. A student made up the following analogy for resonance stabilization: "*A kid lives on a block with very few fences separating the back yards. The larger the number of yards he and the other kids have access to, the happier they are.*"

a. Explain what each underlined element of the analogy represents in terms of chemistry.

A second student thinks this analogy is incomplete. She adds: "*To figure out the happiness of a kid you must consider both the number of yards he has access to and the quality of the grass in each yard.*"

b. What does *the quality of the grass in each yard* represent in terms of chemistry?

19. Read the assigned sections in your text and do the assigned problems.

The Big Picture

The main point of this activity is to build your skill at drawing resonance structures. Do as many practice problems as you can to put the rules for drawing resonance structures to the test.

Common Points of Confusion:

- It is critical to recognize that (baring a key exception) YOU CAN ONLY DRAW MULTIPLE RESONANCE STRUCTURES OF A MOLECULE IF IT HAS EITHER A +1 OR -1 FORMAL CHARGE, AND AN ADJACENT PI BOND. That is to say, a molecule with all zero formal charges rarely has multiple resonance forms. Many students assume that any molecule containing a double bond can experience resonance stabilization—this is incorrect. A possible source of this misconception is the fact that benzene and other aromatic molecules do have multiple (usually two) resonance forms. Do not let this exception cloud your comprehension of the rule in ALL CAPS which leads off this bullet.

- A good way to approach drawing resonance structures is to consider that the "purpose" of drawing resonance structures is (usually) to show that a +1 or -1 charge can be "moved" to different atoms in the molecule. (Resonance structures show what atoms share a delocalaized charge.) With this in mind, each set of curved arrows, used to generate the next resonance structure in a series, should move a formal charge to a new location.

- **Tricks for checking your resonance structures**:

  - Count your H's. You cannot break any single bonds, so there must be the same arrangement of H's on ALL your resonance structures. The most common error drawing resonance structures is to lose, gain, or move an H.

  - If you start with exactly one -1 charge on your first r.s., each r.s. must have exactly one -1 charge on it. Same goes for +1 charges. Do not change the total number or type of charges.

- Students memorize that carbon with a -1 charge is high in PE and therefore unfavorable. This makes some incorrectly infer that a resonance structure with a negative charge on carbon will actually raise the PE of a system. As the postal workers analogy on the previous page is supposed to convey, a resonance structure only can help lower the PE of an ion.

- It is very common for beginning students to say that resonance structures that look like mirror images of each other (or rotated versions of one another) are the same, redundant, and therefore it is not necessary to draw them. This is incorrect. For example, in the last two CTQ's of this activity, the five resonance structures of cyclopentadienyl anion look like the same resonance structure, just rotated 1/5 of a turn each time, BUT all five resonance structures are unique and necessary for a complete picture of the ion. This seeming contradiction comes about because the drawing of resonance structures is a thought experiment in which you claim to be able to pin down the molecule in space and identify individual atoms even if they are otherwise identical. This is done with x, y, and z labels for bicarbonate in Model 2; the x and y oxygens are indistinguishable from one another without the labels. (Though the z oxygen is different since it is attached to an H.)

- Soon we will start using skeletal structures where the H's are not drawn but assumed. The number one error that organic students make when drawing resonance structures is to lose track of the number of H's attached to a given atom. As a temporary crutch, it may help to sketch in the H's as you get used to the skeletal structures.

Nomenclature Worksheet 1

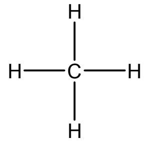
NAMING ALKANES AND CYCLOALKANES

Model 1: Alkane Nomenclature

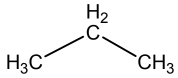
alkane = molecule consisting entirely of carbon and hydrogen atoms connected by single bonds

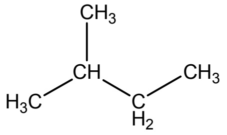
Critical Thinking Question

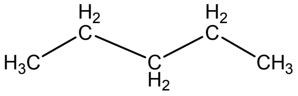
1. Cross out each molecule below that is NOT an alkane.

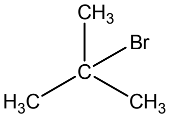


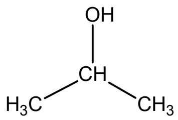
H_3C-CH_3



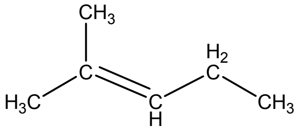


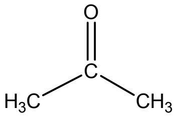






CH_3Cl





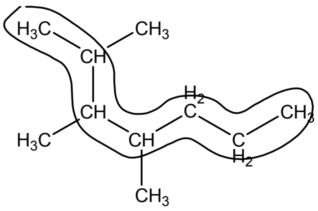
Memorization Task NW1.1: Memorize the names of the straight-chain alkanes below

#C's	Condensed Structure	Name
1	CH_4	**meth**ane
2	CH_3CH_3	**eth**ane
3	$CH_3CH_2CH_3$	**prop**ane
4	$CH_3CH_2CH_2CH_3$	**but**ane
5	$CH_3CH_2CH_2CH_2CH_3$	**pent**ane
6	$CH_3CH_2CH_2CH_2CH_2CH_3$	**hex**ane
7	$CH_3CH_2CH_2CH_2CH_2CH_2CH_3$	**hept**ane
8	$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_3$	**oct**ane
9	$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_3$	**non**ane
10	$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_3$	**dec**ane

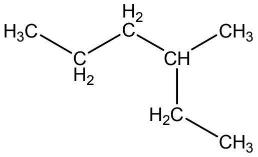
Critical Thinking Questions

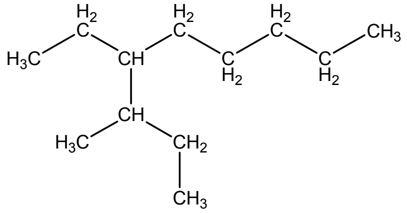
2. (E) Write a correct name below each of the unbranched alkanes in CTQ 1.
3. (E) What suffix do all the names in Model 1 have in common with each other?
4. (E) What prefix stands for eight carbons?

5. **parent chain** = longest continuous chain found in a branched molecule. Circle and name the parent chain in each molecule below. The first one is done as an example.



Parent chain = heptane

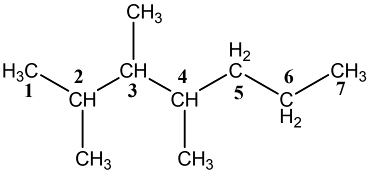




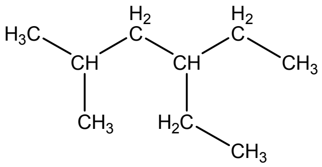
6. A molecule can have more than one parent chain of equal length. Mark the alternate seven-carbon parent chain in the heptane example molecule above. *(In this case, the two parent chains are equivalent, but as we will see later on, it sometimes matters which parent chain you choose.)*

Model 2: Naming Branched Alkanes (Alkyl Groups)

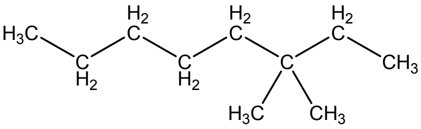
The parent chain name serves as the main part of the name of a branched alkane. For example:



2,3,4-trimethylheptane



4-ethyl-2-methylhexane



3,3-dimethyloctane

Critical Thinking Questions

7. Number the carbons in each parent chain in the structures in Model 2. By convention, numbering of a parent chain starts from the end nearest a branch. (The first one is done for you.)

8. Underline the parent name in each chemical name in Model 2, and confirm that the parent chain matches this name. (The first one is done for you.)

9. According to the examples in Model 2, what word in a name signifies a…

   a. one-carbon branch?

   b. two-carbon branch?

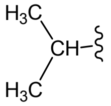
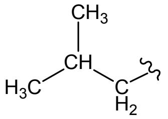
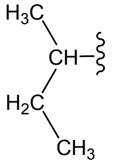
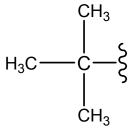
10. Use Model 1 to propose names for three-, four-, five-, and six-carbon branches that follow the same pattern as "methyl" and "ethyl" for one- and two-carbon branches, respectively. *(Note: The names of seven-, eight-, etc. carbon branches follow the same pattern, but branches of such length are rare since they are usually the parent chain.)*

11. What information do the numbers in the names in Model 2 convey?

12. What do the words "di" and "tri" in the names in Model 2 convey?

13. (Check your work.) Do your answers to CTQ 10 fit the data in Memorization Task NW1.2 below?

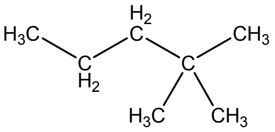
Memorization Task NW1.2: Names of commonly found branches ("alkyl groups")

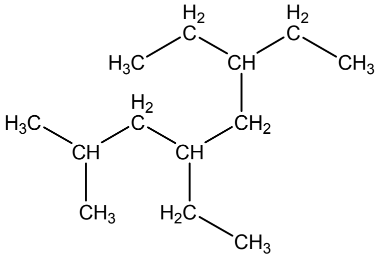
# C's	**Structure**	**IUPAC Name**	**Alternate IUPAC Name**
1	$-CH_3$	**meth**yl	
2	$-CH_2CH_3$	**eth**yl	
3	$-CH_2CH_2CH_3$	**prop**yl	*n*-propyl or propan-1-yl
3		iso**prop**yl	propan-2-yl
4	$-CH_2CH_2CH_2CH_3$	**but**yl	*n*-butyl or butan-1-yl
4		iso**but**yl	2-methylpropan-1-yl
4		*sec*-**but**yl	butan-2-yl
4		*tert*-**but**yl	*t*-butyl *(looks like a T!)* or 2-methylpropan-2-yl
5	$-CH_2CH_2CH_2CH_2CH_3$	**pent**yl	pentan-1-yl

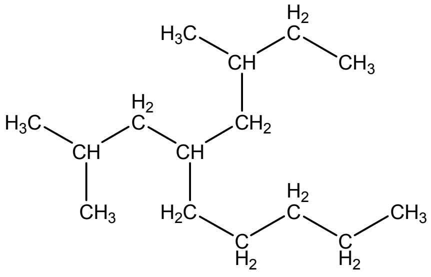
Multiple different branches are listed in a name **alphabetically** (not including prefixes di, tri, *sec,* or *tert*).

Critical Thinking Questions

14. Name the following alkanes.







15. (Check your work.) Explain what is wrong with each of the following names for the first molecule above:

 a. 4,4-dimethylpentane

 b. 1,1,1-trimethylbutane

 c. 2,2-methylpentane

 d. 2-dimethylpentane

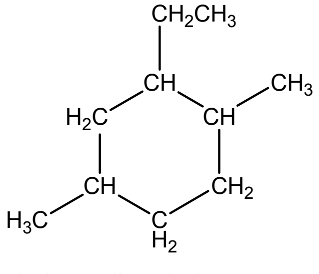
16. (Check your work.) Explain what is wrong with each of the following names for the third molecule in CTQ at the bottom of the previous page.
    a. 6-ethyl-2-methyl-4-pentyloctane
    b. 3-methyl-5-isobutyldecane (*Hint*: Read the rule at the bottom of Memorization Task NW1.2)

17. Draw the following alkanes
    a. 2,3,3-trimethylpentane
    b. 3-ethyl-2,5-dimethylhexane

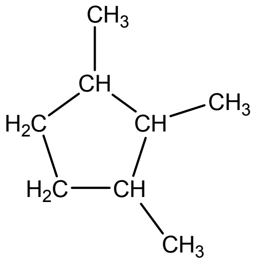
Model 3: Cyclic Alkanes

- If a ring is present in a molecule, this ring almost always is considered the parent chain.
- Number alkyl groups starting with one, and number around the ring toward the closest group.
- If there are exactly two alkyl groups, decide which gets “1” based on alphabetical order.

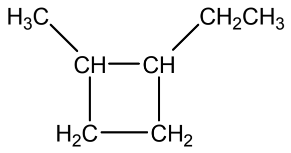
Examples



2-ethyl-1,4-dimethyl**cyclohexane**



1,2,3-trimethyl**cyclopentane**



1-ethyl-2-methyl**cyclobutane**

Critical Thinking Questions

18. What prefix is used to indicate that a parent chain (e.g., hexane) is cyclic?

19. Draw structures that correspond to the following names:

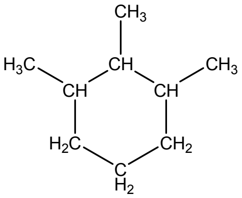
a. 3-methylhexane b. 1,1-diethylcyclobutane c. 1-*t*-butyl-4-methylcyclohexane

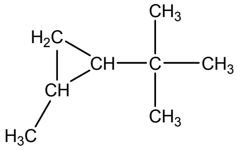
20. For mono-substituted cycloalkanes the “1” is not included. That is, the name 1-methylcyclohexane is not correct. The correct name is simply “**methylcyclohexane**”.

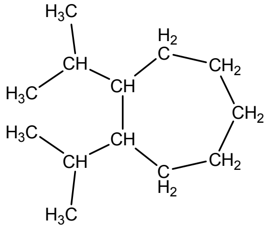
    a. Draw methylcyclohexane.

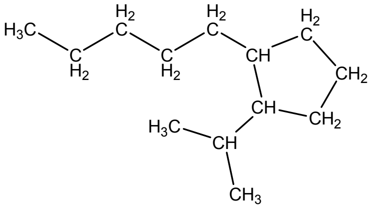
    b. Explain why adding a “1” to methylcyclohexane does not add any new information.

21. Write a correct name for each of the following structures:



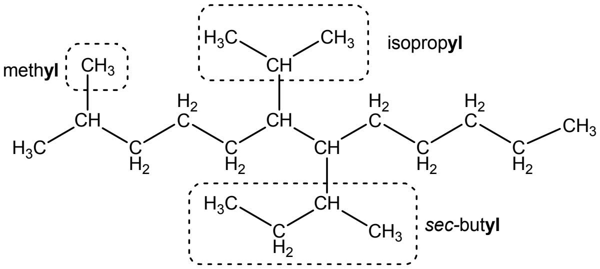




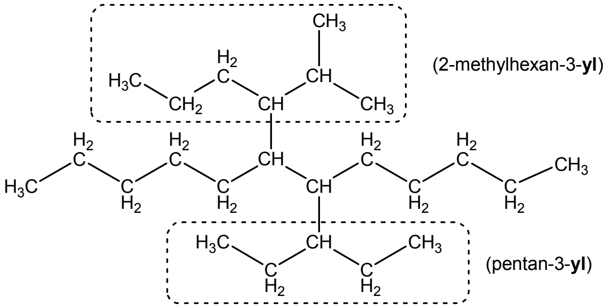


Model 4: Alternate IUPAC Strategy for Naming Alkyl Sidechains

side chain = a group that is not part of the parent chain. Side chains are boxed in the diagram below.



7-*sec*-butyl-6-isopropyl-2-methyldodecane



6-(2-methylhexan-3-yl)-7-(pentan-3-yl)dodecane

Critical Thinking Questions

22. What two-letter suffix appears to be common to the names of all side chains?

23. On the right-hand structure, what information is conveyed by the number preceding each “yl”?

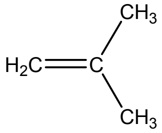
24. Next to the isopropyl and *sec*-butyl side chains above, write their names based on the alternate naming strategy used to generate the names (2-methylhexan-3-yl) and (pentan-3-yl).

25. Is your answer to the previous question consistent with the last column in Mem. Task NW1.2?

26. Write the name of the molecule on the left using alternate side chain names (where applicable).

Exercises

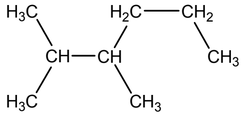
1. Construct an explanation for why the following molecule is called methylpropene instead of 2-methyl-1-propene.

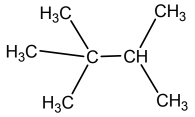


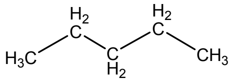
methylpropene

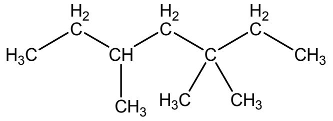
2. Draw the following molecules:
   - a. 2,2,3,3-tetramethyl-6-propyldodecane
   - b. 2-methyl-3-ethyl-4-isobutyldecane
   - c. *tert*-butylcyclopentane
   - d. 4-*t*-butyl-2,6-dimethylheptane
   - e. 4-isopropylheptane
   - f. 2,3-dimethyl-4-propyloctane
   - g. 6-(3-methylbutan-1-yl)-7-(2-methylpentan-2-yl)-4-(propan-2-yl)dodecane
   - h. 4,4-dimethyl-5-(2,4-dimethylpentan-3-yl)decane
   - i. 1,3,5-trimethylcyclohexane
   - j. (3-propylheptan-2-yl)cyclohexane

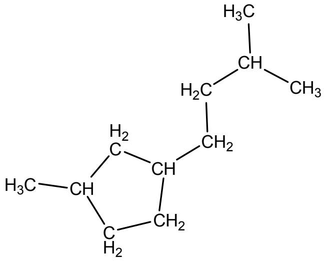
3. Name each of the following structures.

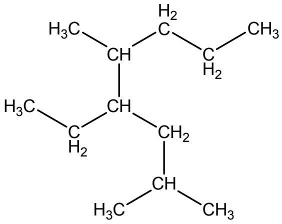


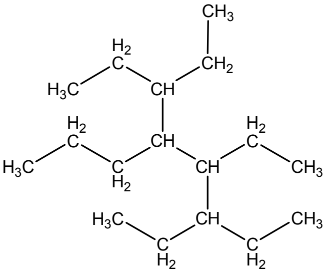


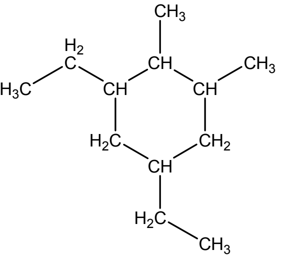












ChemActivity 6: Alkanes and Alkenes

BUILD MODELS: CH_3CH_3 *AND* $CH_3CH_2CH_2CH_3$

While you wait for class to begin, make a model of each molecule in the "BUILD MODELS" section.

PART A: CONFORMERS OF ALKANES

(What is the lowest-energy conformation of butane?)

Model 1: Lowest P.E. Conformation of Ethane (CH_3CH_3)

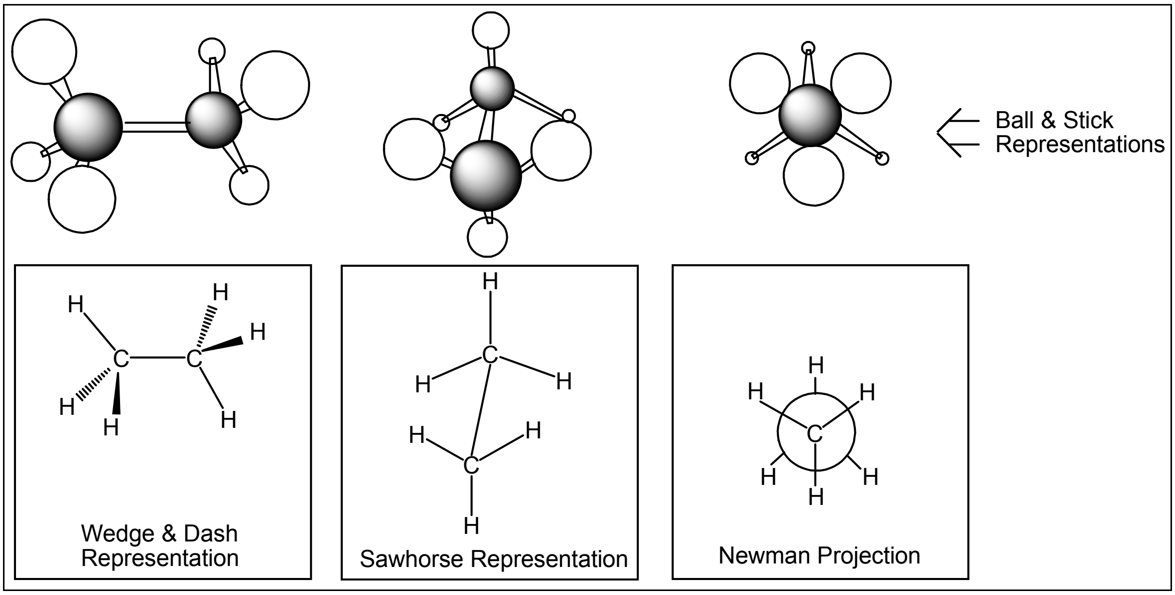


Figure 6.1: Ethane in the Staggered Conformation

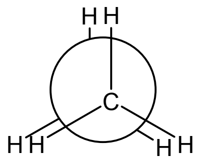
Each representation above shows ethane (CH_3CH_3) in its lowest P.E. (most favorable) **conformation**.

Critical Thinking Questions

1. (E) Make a model of ethane. Each time you move atoms by rotating a single bond you are changing the **conformation** of the molecule. Rotate the C—C single bond of butane to put it in its most favorable conformation (as shown in Model 1). This conformation is called **staggered**.

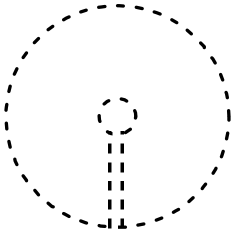
2. The conformation at right is called **eclipsed**. It is the least favorable (highest P.E.) conformation of butane.

   a. (E) Explain the names **staggered** and **eclipsed.**



Newman Projection of Eclipsed Conformation

   b. Construct an explanation for why the staggered conformation is more favorable than the eclipsed conformation. (Both are "**conformers**" or "**conformational stereoisomers**" of ethane.)



3. Newman projections are confusing partly because an imaginary disc is inserted in the drawing to create the illusion of near and far.
    a. Tear or cut out a piece of paper the shape of this object →
    b. Hold your eye up to your model of ethane to simulate the perspective shown by the Newman projection in Figure. 6.1.
    c. Hang your cut-out shape on the C—C bond of your model of ethane to serve as the disc shown in every **Newman projection**.
    d. Identify the single atom of ethane that is hidden from view behind this disc in the drawing (and now in your model).

Model 2: Potential Energy (P.E.) Revisited

Recall our analogy between chemical **potential energy** and gravitational potential energy.

In the diagram below a marble moves from high to low P.E.. As in most chemical systems, the **spontaneous** change from high to low P.E. is accompanied by the release of heat.

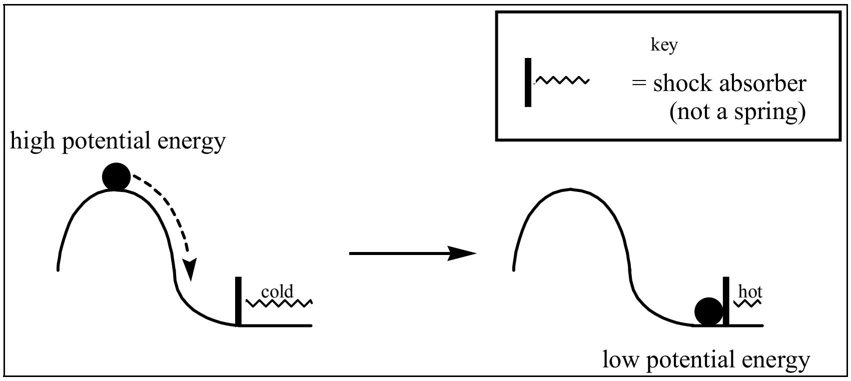


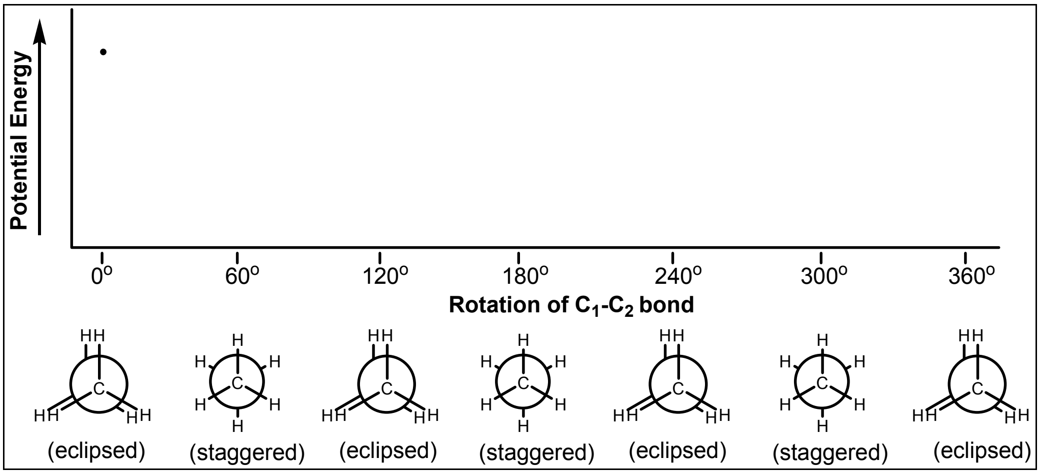
Figure 6.2: High and Low Potential Energy Marble

Critical Thinking Questions

4. (E) In which location is the marble more stable (unlikely to change position)?

5. In general, **high potential energy** systems are **unstable** and **likely to change** ***if they have a way to change***. Because single bonds can rotate freely, ethane in the eclipsed (highest P.E.) conformation is not stable (see Newman Projection in CTQ 2).
    a. (E) What conformation of ethane is “downhill” in terms of potential energy from the eclipsed conformation?
    b. What repulsive force(s) will cause ethane in the eclipsed conformation to quickly adopt the conformation you cited above?

6. Complete this graph of *relative* **potential energy** vs. **rotation of the C_1–C_2 bond** of ethane. The point drawn for you indicates the P.E. at 0^o (eclipsed).



Model 3: Ethane in Motion

At room temperature, the C_1-C_2 bond of ethane is spinning rapidly. If you could observe this spinning closely you would see that the molecule zips past the high-energy eclipsed conformations and slows down to take advantage of the low-energy staggered conformations. Chemists explain this phenomenon by saying that the molecule gets stuck in the **potential energy wells** of the staggered conformations. (These wells are the valleys on your diagram above.)

Critical Thinking Question

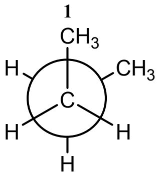
7. If you could devise a way to take an instantaneous snapshot of ethane, in what conformation would you be most likely to "catch ethane?" Explain your reasoning.

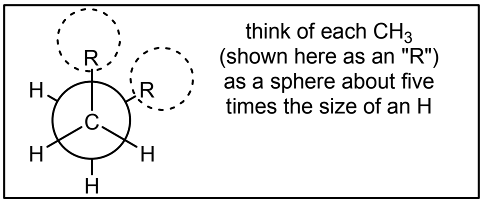
Model 4: Newman Projections of Butane ($CH_3CH_2CH_2CH_3$)

A **Newman projection** of a molecule focuses on rotation of one bond. In the example below it is C_2-C_3, so we ignore the rotation of all other bonds.

For simplicity, we treat groups attached to C_2 or C_3 as R groups.

staggered conformation with methyl groups **gauche** to one another

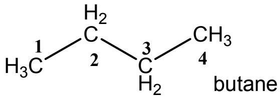




think of each CH_3 (shown here as an "R") as a sphere about five times the size of an H

Critical Thinking Questions

8. Make a model of butane and put it in the conformation shown in Model 4.



   a. Locate C_2, C_3 and C_4 in Model 4.

b. Have each member of your group sight down the C_2—C_3 bond of a model to simulate the perspective shown by the Newman projection in Model 4.

9. The conformation shown in Model 4 is a special type of **staggered conformation** in which the two methyl groups are neighbors (60^o apart). This is called the **staggered-gauche** conformation. It is NOT the most favorable conformation (nor the least favorable conformation).

a. Draw a Newman Projection of butane showing the C_2-C_3 bond in its most favorable conformation**.** **(Show CH_3 groups as "R")**

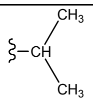
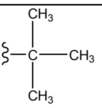
b. This most favorable (lowest potential energy) conformation which you drew in part a is called **staggered-anti**. Construct an explanation for both parts of this name.

Model 5: Alkyl Groups (R groups)

Butane is a straight four-carbon chain. For drawing a Newman projection it was convenient for us to think of the CH_3 at either end of the chain as an R group. This same strategy can be used to simplify Newman projections of more complicated molecules.

alkyl group = group consisting of C and H connected by single bonds and designated by "R"

Memorization Task 6.1: Memorize the names and structures of common alkyl (R) groups

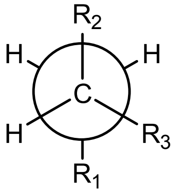
Condensed Structure	**Structure (if branched)**	**Name of R Group (abbreviations)**
$-CH_3$		methyl group (Me)
$-CH_2CH_3$		ethyl group (Et)
$-CH_2CH_2CH_3$		propyl group (Pr or *n*-Pr) *n* = "normal"
$-CH(CH_3)_2$		isopropyl group (*i*-propyl, or *i*-Pr)
$-CH_2CH_2CH_2CH_3$		butyl group (Bu or *n*-Bu) *n* = "normal"
$-C(CH_3)_3$		*tertiary*-butyl group (*tert*-butyl or *t*-butyl)

Memorization of the parent names, meth, eth, prop, but, etc., is the starting point for learning the rules for naming all organic molecules. These rules can be found in Nomenclature Worksheet 1 (NW1).

Critical Thinking Questions

10. Consider the Newman projection below.

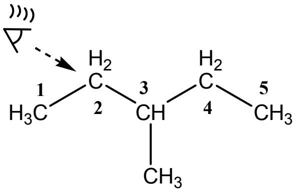
    a. Draw a full Lewis structure of this molecule with R_1 = Me, R_2 = Et, and R_3 = *i*-Pr.



    b. Given the sizes of these R groups ($R_3 > R_2 > R_1$), does the Newman projection above show the lowest potential energy conformation of this bond? If not, draw a Newman projection showing the lowest P.E. conformation (sighting down this same bond).

    c. To draw a Newman projection in the lowest P.E. conformation, the following rule of thumb usually applies: *Place the largest group on the front carbon* ***anti*** *to the largest group on the back carbon*. Is your answer to the previous question consistent with this rule of thumb?

11. Draw a Newman projection showing the lowest P.E. conformation of the following molecule sighting down the C_2—C_3 bond (as indicated below). Show methyl and ethyl groups as Me and Et.



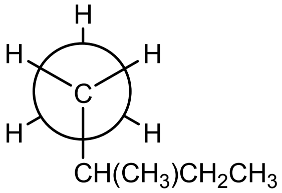
Only the carbons in the longest chain receive a number.

12. An R group that is not common enough to have an abbreviation should be represented on a Newman projection using its **condensed structure**, as in the following example:

    a. Confirm that the Newman projection at right is a representation of the molecule in the previous question.

    b. Label carbons 1-5 on the Newman projection at right (being sure to indicate which C is hidden behind the imaginary "disk").

    c. Add to the Lewis structure in the previous question a drawing of an eye and a dotted arrow indicating the sight line represented by the Newman projection at right.

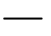
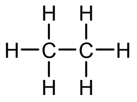
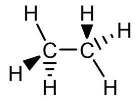
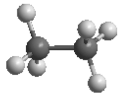
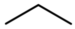
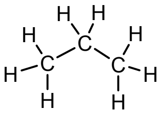
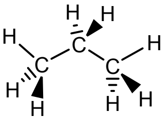
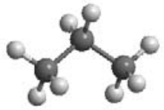
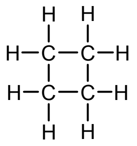
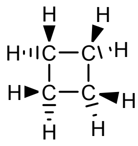
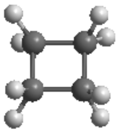
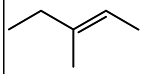
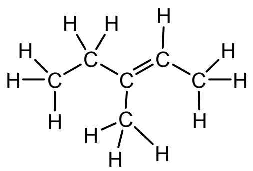
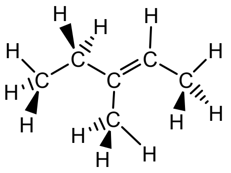
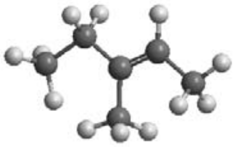
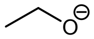
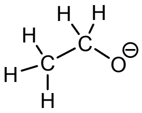
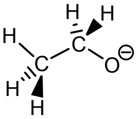
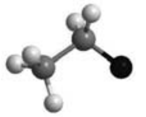


BUILD MODELS: $CH_3CH_2CH_2CH_2CH_2CH_3$

PART B: CONSTITUTIONAL ISOMERS

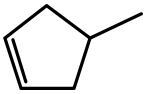
(Are two molecules with the same molecular formula the same/conformers or **constitutional isomers**?)

Model 6: Representations of Carbon Structures

Skeletal	Bond-Line	Wedge & Dash	Ball & Stick	Condensed
				CH_3CH_3
				$CH_3CH_2CH_3$
				$(CH_2)_4$
				$CH_3CH_2CCH_3CHCH_3$
				$CH_3CH_2O^-$

Critical Thinking Questions

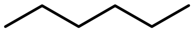
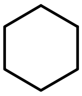
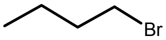
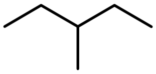
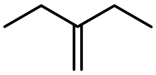
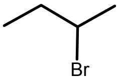
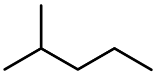
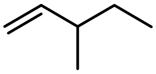
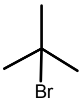
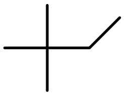
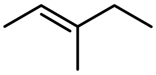
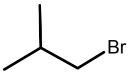
13. (E) Draw a bond-line representation of the molecule shown below as a skeletal representation.



14. In skeletal representations the hydrogens are not shown. Is it still possible to tell how many hydrogens there are on a particular carbon? If so, explain how.

15. (E) If you know the formal charge of an atom in a structure, you can tell how many lone pairs are on that atom. If you know how many lone pairs are on the atom, you can determine its formal charge. Up to this point, both have been shown. However, by convention **only one is required**. Based on Model 6, which is required to be shown, an atom's formal charge or its lone pairs?

Model 7: Constitutional Isomers

Column 1		Column 2		Column 3	
structure	molecular formula	structure	molecular formula	structure	molecular formula
	C_6H_{14}		C_6H_{12}		C_4H_9Br
	C_6H_{14}		C_6H_{12}		
	C_6H_{14}				
					

Critical Thinking Questions

16. (E) Complete the table in Model 7 by writing in the missing molecular formulas.

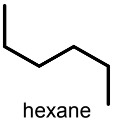
17. What do the molecules in a given column (1 or 2 or 3, above) have in common with the other molecules in that same column?

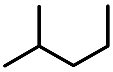
18. Describe the differences among the four molecules in a given column.

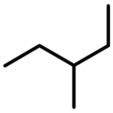
19. All the structures in a given column are **constitutional isomers** of one another, but the structures in column 1 are not constitutional isomers of structures in other columns. Based on this information, write a definition for the term **constitutional isomers** that starts:
"Two molecules are constitutional isomers if..."

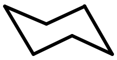
20. Without breaking bonds, change your model of hexane from the conformation shown in Model 7 to the one shown in the bottom left corner of this page.

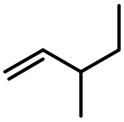
21. Each structure below is an alternate representation of a structure in Model 7. Under each structure, draw the structure from Model 7 that represents the same molecule. *Recall that:* ***Two molecules are the same if models of each can be interconverted without breaking bonds*** *(i.e., they are conformers).*

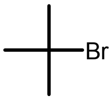

hexane

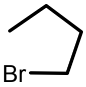






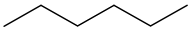
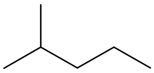
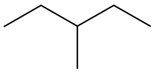
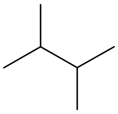
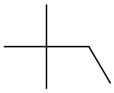
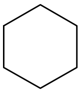
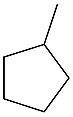






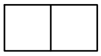
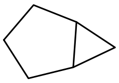
22. Draw five constitutional isomers missing from Column 2 in Model 7. (There are more than five.)

23. Shown below are a handful of the possible six-carbon backbones (i.e., the ways six carbons can be arranged). If the previous question asked you to draw ALL missing constitutional isomers, a good way to start would be to draw all possible "backbones," then add double bonds as needed.

a. Circle the backbones above that need a double bond to become a constitutional isomer of the molecules in **Column 2** of Model 7.

b. Explain why the following arrangements of six carbons CANNOT form the backbone of a constitutional isomer of the molecules in Column 2 of Model 7.

c. T or F: All constitutional isomers of the molecules in Column 2 will have exactly one double bond or one ring.

Memorization Task 6.2: Molecular formula of a *saturated* alkane = C_nH_{2n+2} *(where n = no. C's)*

alkane = molecule with only C/H, and no π bonds or rings, e.g., pentane [CH_3-CH_2-CH_2-CH_2-CH_3] (Note: pentane has two H's for each C, plus one extra H on each end C, thus no. H's = 2 x no. C's + 2.)

Critical Thinking Questions

24. Draw a constitutional isomer of pentane, and explain why branching does not change the ratio of C to H (the molecular formula remains C_5H_{12}).

25. How many H's are lost from the molecular formula of pentane if a double bond is introduced (changing the parent name of the molecule to pent**ene**)?

26. How many H's are lost from the molecular formula of pentane if the ends are joined into a ring (changing the parent name of the molecule to **cyclo**pentane)?

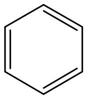
Model 8: Degree of Unsaturation

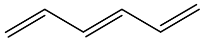
Because π bonds and rings have the same effect on the molecular formula of a molecule (lose two H's), the total number of π bonds and rings in a molecule is given a name…

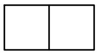
degree of unsaturation = [no. of π bonds] + [no. of rings]

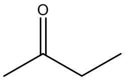
Critical Thinking Questions

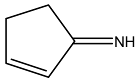
27. Write the degree of unsaturation below each structure.









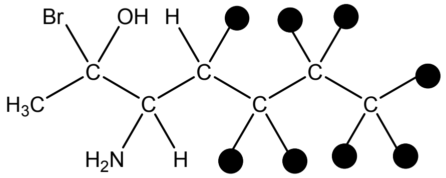


$H_3C—C\equiv C—CH_3$

Memorization Task 6.3: Determining Degree of Unsaturation from Molecular Formula

If you are given only the molecular formula of an unknown molecule (e.g., C_7H_8NOBr) and asked to find the molecule's **degree of unsaturation** (or to draw a possible structure of the molecule)…

I. Draw **any** straight-chain structure containing all the atoms but with no π bonds or rings.
(It doesn't matter where you put the groups as long as each atom has the correct number of bonds.)



● = location of an H ***if the molecule were saturated***

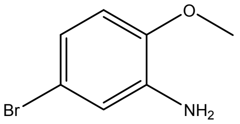
II. Count the number of H's it would take to "saturate" the molecule with H's. (This always will be an even number—if it is an odd number you have made an error.)

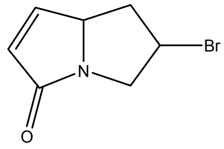
$$\textbf{degree of unsaturation} = \frac{\text{No. of "missing" H's}}{2}$$

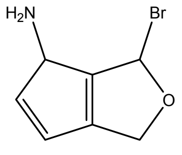
Critical Thinking Questions

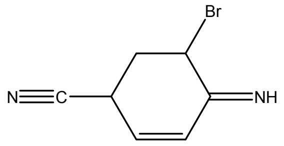
28. What is the degree of unsaturation for the example molecular formula C_7H_8NOBr?

29. **Without counting hydrogens**, determine which one of the following CANNOT be the unknown molecule with molecular formula C_7H_8NOBr, and explain your reasoning.









30. Determine the degree of unsaturation (and draw a possible structure) for a molecule with molecular formula $C_6H_4O_2$

BUILD MODELS: $H_3C—CH=CH—CH_3$

PART C: ALKENE STEREOISOMERS (*E/Z* AND *trans/cis*)

(How can you tell which **stereoisomer** of an *E/Z* pair is *E* and which is *Z*?)

Model 9: 2-Butene

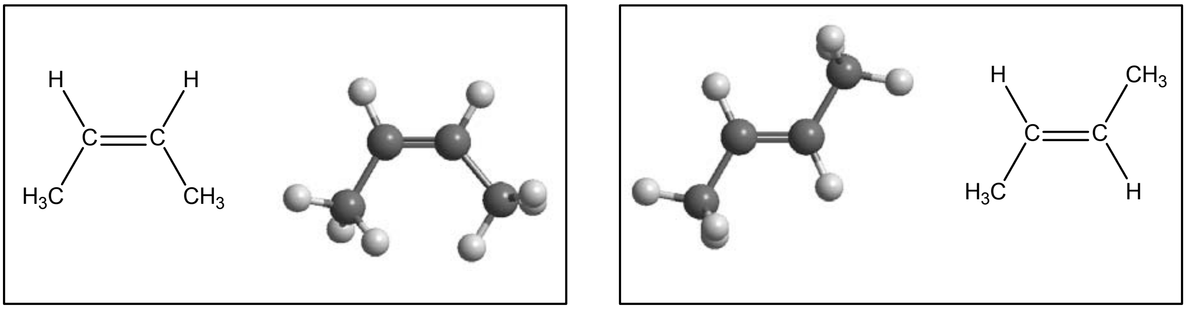


Figure 6.3: Representations of 2-butene molecules

Critical Thinking Questions

31. Make a model of each molecule shown above: Is the molecule in the left box the **same molecule** as the molecule in the right box? Use your models to answer the question, and recall that…

Two molecules are the same if models of each can be interconverted without breaking bonds.

Model 10: *E, Z,* or Neither?

The π portion of a double bond prevents rotation. As a result, many double bonds have two different orientations that give rise to two different molecules.

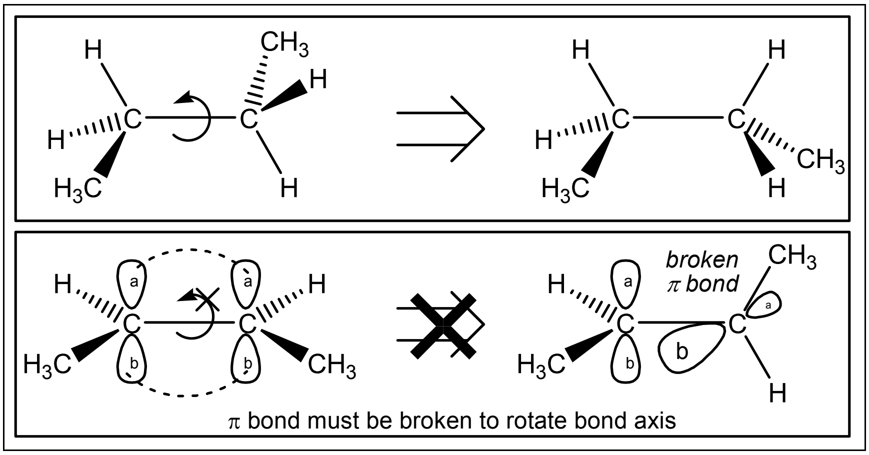


Figure 6.4: Single bonds rotate freely, but double bonds do not.

The letters *E* and *Z* (or the terms *trans* and *cis*) are used to name the two possibilities that result.

Rules for determining *E* and *Z* are on the next page.

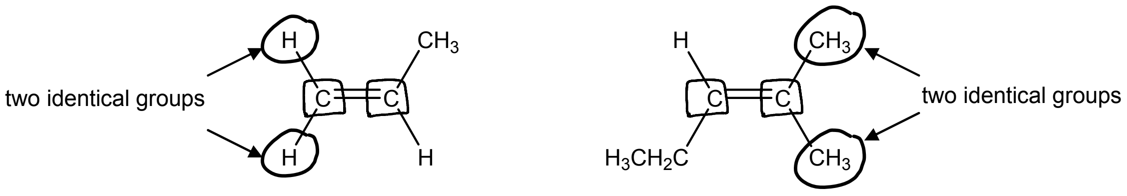
Memorization Task 6.4: Memorize the definitions of *E* and *Z* (and *trans* and *cis*)

To determine if a double bond is **E, Z, or neither**…

I. Put a box around each carbon involved in the double bond (as shown below)

II. Are there two identical groups on *either* boxed C? → If *YES* double bond is neither *E* nor *Z*

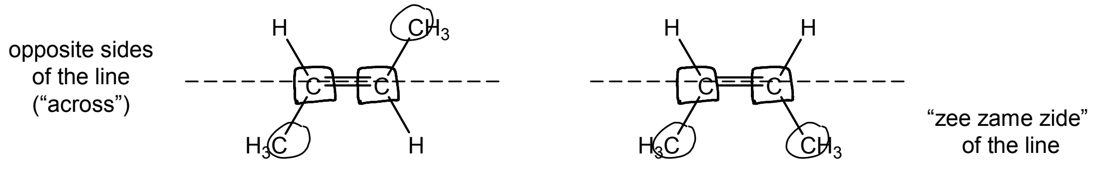
(If a double bond is ***neither*** *there is only one way to draw the molecule, and its name will not include either letter.)*



Neither *E* nor *Z* Neither *E* nor *Z*

STOP here if neither E nor Z

III. Otherwise, draw a dotted line along the double bond, and **circle the atom with the highest atomic number on each boxed C**. *(Atomic numbers from the periodic table: H = 1, C = 6, N = 7, O = 8, etc.).*


opposite sides of the line ("across")
H
CH_3
C
C
H_3C
H
H
H
C
C
H_3C
CH_3
"zee zame zide" of the line

E (or *trans*) *Z* (or *cis*)

- If circled groups are on opposite sides of this line → double bond is ***E***
  E stands for *entgegen*, which is German for "opposite."
- If circled groups are on the **same side** of this line → double bond is ***Z***
  Z stand for *zusammen*, German for "together." (Say it in a German accent "*zee zame zide*")

Trans and *Cis*: alternates for *E* and *Z*

The two circled groups in the *E* molecule above are said to be *trans* to each other. (*trans* = "across")

The two circled groups in the *Z* molecule are *cis* to each other. (Say *cis* with a German accent: "***Z****is*")

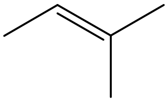
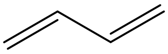
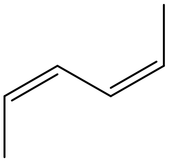
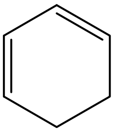
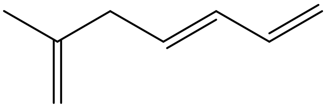
trans and **cis** are often used in place of *E* or *Z* when the groups that are *trans* or *cis* to each other are identical (as in each example above in which both circled groups are methyl groups).

Critical Thinking Questions

32. Label each 2-butene molecule in Model 10 with the appropriate two names. Choose from: *Z*-2-butene*, E*-2-butene, *cis*-2-butene, and *trans*-2-butene.

33. Draw skeletal representations (see Model 6) of *Z*-3-hexene and *E*-3-hexene.
(As described in Nomenclature Worksheet 1… "3-hexene" is $CH_3CH_2CH{=}CHCH_2CH_3$)

34. Label each double bond *E, Z*, or neither. (It may help to draw in some missing H's.)

Model 11: CAHN-INGOLD-PRELOG RULES for Assigning *E/Z* Priorities

The rules for assigning priority outlined in this activity are called the Cahn-Ingold-Prelog rules after their three co-inventors.

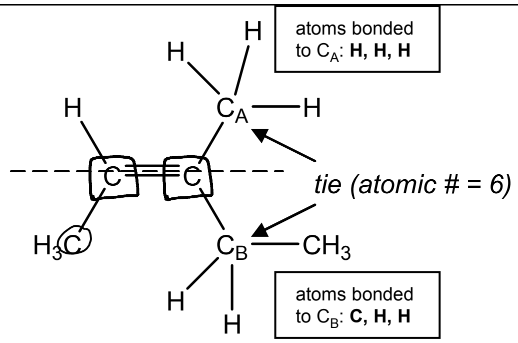
In the structure at right, carbons C_A and C_B are tied.

To determine which gets circled, look at the 3 atoms (other than the boxed carbon) that are bonded to each.

Think of these atoms as "cards."

- C_A's "cards" = H H H
- C_B's "cards" = H H **C**

High card wins, so C_B beats C_A, and the molecule is *Z*.


H
H
H
atoms bonded to C_A: **H, H, H**
H
C_A
H
C
C
tie (atomic # = 6)
H_3C
C_B
CH_3
H
H
atoms bonded to C_B: **C, H, H**

Additional Rules:

isotopes → the heavier atom wins (D beats H)

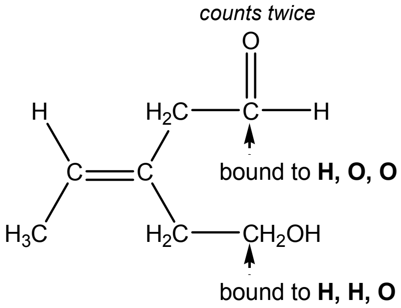
multiple bonds → double bond (e.g., C=O) counts the same as two single bonds to that atom (O-C-O)

If a tie results after the first round of the card game, play a 2nd round using the highest card from each hand.

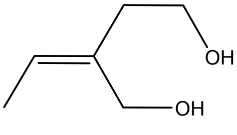
Keep playing until an assignment of *E* or *Z* is made.

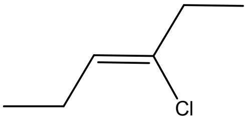
Critical Thinking Questions

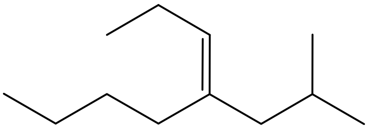
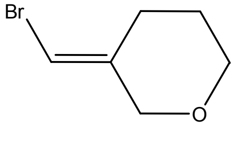
35. Explain why the molecule at right is *E*.



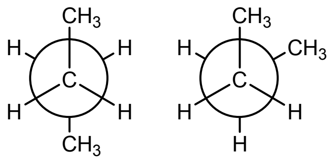
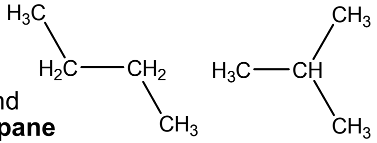
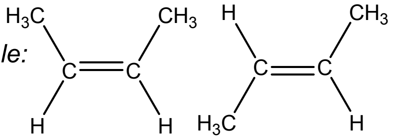
36. Label each molecule below *E, Z*, or neither.





Model 12: Configurational Stereoisomers

*Conformers **(conformational stereoisomers)** can be interconverted via single bond rotation (that is, without breaking bonds). **Conformers** are alternate representations of the **same molecule**.	*For example:* **anti** and **gauche** butane  CH3 H H C H H CH3 CH3 H CH3 C H H H
Constitutional Isomers have the same molecular formula but **different atom connectivity**	*For example:* **butane** and **2-methylpropane** 
****Configurational Stereoisomers** (*some books call these "**stereoisomers**" for short)* have the same molecular formula AND the same atom connectivity, but **CANNOT be interconverted via single bond rotation**.	*For example:* ***Z*** and ***E***-2-butene  H3C CH3 C C H H H CH3 C C H3C H

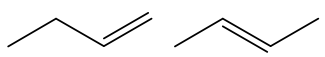
You cannot buy a bottle of "anti" butane or "gauche" butane because in any sample of butane at normal temperatures the molecules are rapidly interconverting among all possible conformations. You can buy a bottle of E-butene or Z-butene.

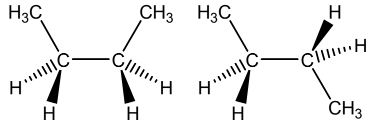
**To avoid confusion between conformational and configurational stereoisomers we will call the former "conformers."*

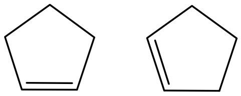
*** Many books erroneously drop the term "configurational" and call configurational stereoisomers simply "stereoisomers" for short. WATCH OUT: The term stereoisomer is often used in place of "configurational stereoisomer."*

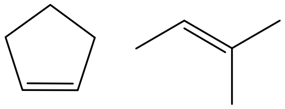
Critical Thinking Questions

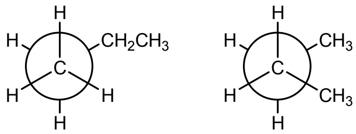
37. Indicate the relationship between each pair. Choose from: **configurational stereoisomers, conformers, constitutional isomers,** or **different formulas**. (Each term is used at least **twice**.)

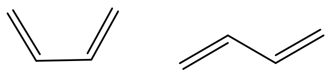


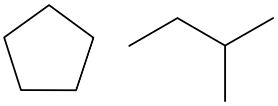


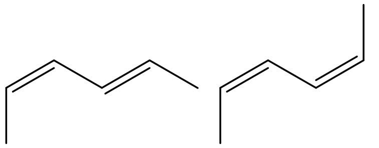


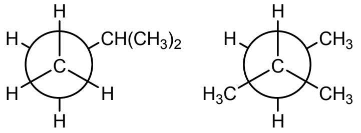


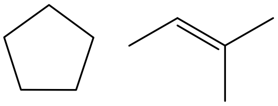


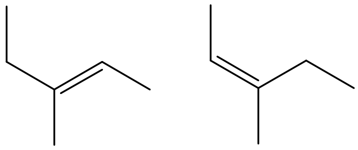


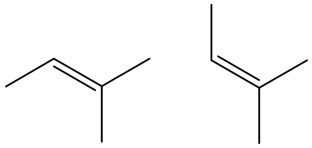










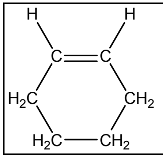


Model 13: ALKENE NOMENCLATURE

Naming can be a great way to figure out the relationship between two molecules. For example: If two molecules have the same name, they are the same or conformers. If two names differ only in the prefixes *Z* vs. *E*, the molecules are configurational stereoisomers.

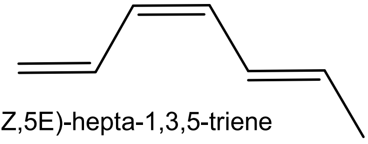
Memorization Task 6.5: Rules and Conventions for Naming Alkenes

- To properly name a molecule with one *Z* or *E* double bond you must include the appropriate prefix before the name (omitting the prefix implies a mixture of *Z* and *E*)
  - An exception to the above: A double bond in a ring is assumed to be *Z* e.g., "**cyclohexene**" not *Z*-cyclohexene.



It is understood that the double bond is *cis* because placing a *trans* double bond in a ring puts tremendous strain on the molecule.

- If there is more than one double bond that is *Z* or *E*, use multiple prefixes and numbers to designate which bonds are *Z* and which are *E*.
  - Molecules with two, three, or four double bonds have the base names "diene," "triene," and "tetraene," respectively.


(3Z,5E)-hepta-1,3,5-triene

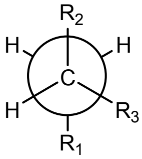
Critical Thinking Questions

38. Name each molecule on the previous page using information found in Model 13 and Nomenclature Worksheet 1.

Exercises for Part A

1. The staggered-gauche conformation shown in Model 4 is not the most favorable or the least favorable conformation of butane. Draw a Newman Projection of butane in its least favorable (highest potential energy) conformation.

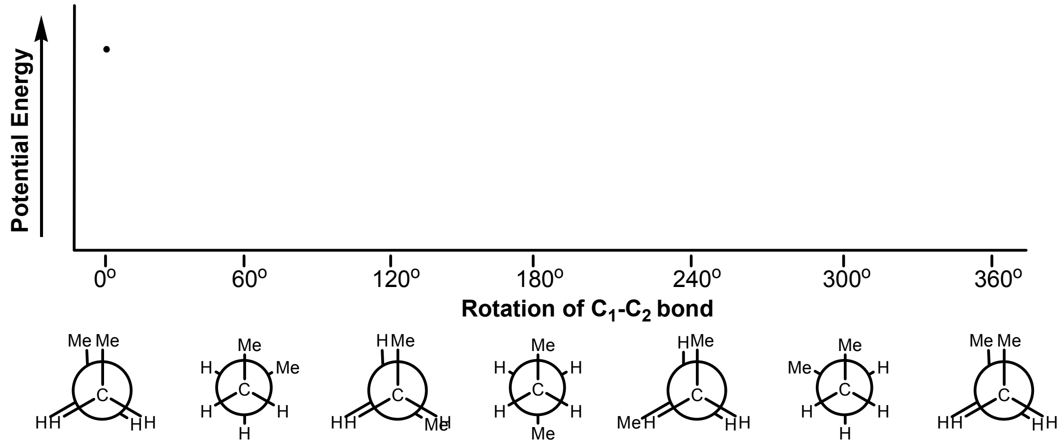
2. The words **anti** and **gauche** can describe a molecule's conformation, or the relative positions of two groups. For example, R_1 and R_2 are **anti** to one another.



   a. Label the H that is **anti** to R_3, and label the H that is **gauche** to R_3.

   b. Which word (**anti, gauche,** or **neither term**) describes the relationship between R_1 and R_3? … R_2 and R_3?

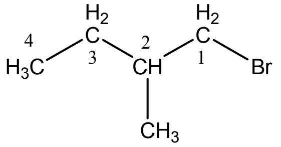
3. Using your model of butane ($CH_3CH_2CH_2CH_3$), complete the following graph of the **angle between the two Me groups** vs. potential energy.



   a. Label each Newman projection of butane on the graph with the words staggered, eclipsed, gauche, and anti, as appropriate. (Note that some structures will have more than one label.)

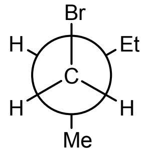
   b. Draw a wedge and dash bond representation of butane in its lowest P.E. conformation.

4. Consider the molecule 1-bromo-2-methylbutane. C_3 and C_4 should be drawn as Et as in the example. This group is called an **ethyl group** and can be considered a sphere about twice the size of a methyl group. Draw the following Newman projections **sighting down the C_1—C_2 bond…**



1-bromo-2-methylbutane

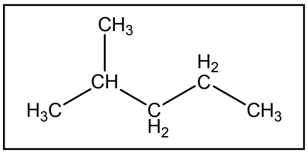
example Newman Projection

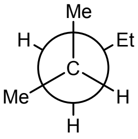


   a. The lowest potential energy conformation**.**

   b. The highest potential energy staggered conformation.

5. Which is a Newman projection of the molecule in the box?

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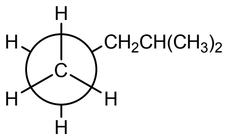
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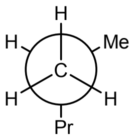
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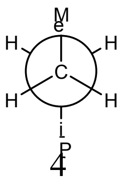

4

6. **Complete Nomenclature Worksheet 1**. By next class you must memorize the rules for naming alkanes and alkenes.

7. Read the assigned sections in your text, and do the assigned problems.

Exercises for Part B

8. Draw the one constitutional isomer that is missing from column 1 of Model 7.

9. Draw skeletal representations of as many constitutional isomers missing from column 2 in Model 7 as you can. (Hint: Other than cyclohexane, there are 11 ways to draw a six-carbon backbone that contains a ring. Plus there are isomers of cyclohexane that do not contain a ring.)

10. Are any constitutional isomers missing from Column 3 in Model 7? (A good way to answer this and similar questions is to start by drawing all possible carbon backbones. Then figure out how many different ways you can add the Br atom, or double bond—as in the previous question—or fluorine—as in the next question.)

11. Draw as many constitutional isomers as you can with the formula $C_5H_{11}F$.

12. Draw the structure of a six-carbon alkene (containing only C and H) with one ring and one double bond.
    a. Draw a constitutional isomer of the structure you drew above with no rings.
    b. Explain the following statement found in many text books: "In terms of molecular formula, a ring is equivalent to a double bond."

13. What is the purpose of CTQ 21? What concept distinction or common misconception is it designed to highlight?

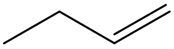
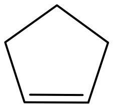
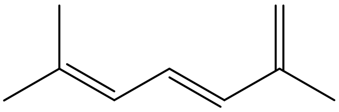
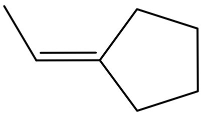
14. Read the assigned sections in your text, and do the assigned problems.

Exercises for Part C

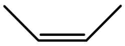
15. Draw a skeletal representation of *Z*-2-hexene and *E*-2-hexene.

16. Draw 1-butene. Why does it not make sense to specify either *Z* or *E* 1-butene while you must specify *Z* or *E* 2-butene to draw the correct molecule?

17. Label each double bond *E (trans)*, *Z (cis)*, or neither. (It may help to draw in critical H's.)

18. Label each double bond *Z*, *E*, or neither.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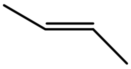
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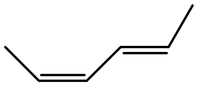
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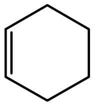
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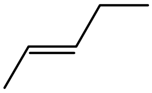
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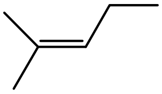
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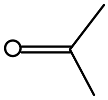
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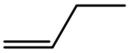
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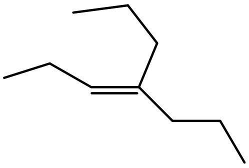
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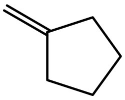

X

a. For each structure draw one constitutional isomer and all possible configurational stereoisomers.

b. A "terminal" double bond is a double bond found at the end of a carbon chain (e.g., VIII and X). What generalization can you make about all "terminal" double bonds in terms of *Z/E* (or neither)?

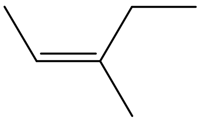
c. What is the relationship between Compounds III and IV above?

19. Draw a skeletal structure of *E*-3,4-dimethyl-3-heptene.

a. Following the algorithm in Memorization Task 6.4 results in two circled groups attached to the carbons involved in the double bond that are not identical. Nevertheless, the molecule still qualifies as *trans* (having two identical groups *trans* to one another). Explain.

b. Draw and name the configurational stereoisomer of *E*-3,4-dimethyl-3-heptene

20. Name this molecule, draw and name its configurational stereoisomer, and construct an explanation for why naming this molecule using *cis* or *trans* (instead of E or Z) could lead to ambiguity.



21. Draw another example of an alkene that cannot be named using the *cis/trans* nomenclature. (Such a molecule is not *cis, trans* or neither, but instead requires the *E/Z* nomenclature.)

a. Draw the configurational stereoisomer of the molecule you drew above. (If it has no configurational stereoisomer, your original structure is not correct.)

b. Describe the characteristics of a molecule that falls outside the *cis, trans* or neither naming scheme and requires the *E/Z* naming scheme.

22. Double bonds do not rotate freely under normal conditions. The change from Z to E requires a reaction. This can occur in the presence of a catalyst or with the addition of a large amount of energy (e.g., at high temperature).

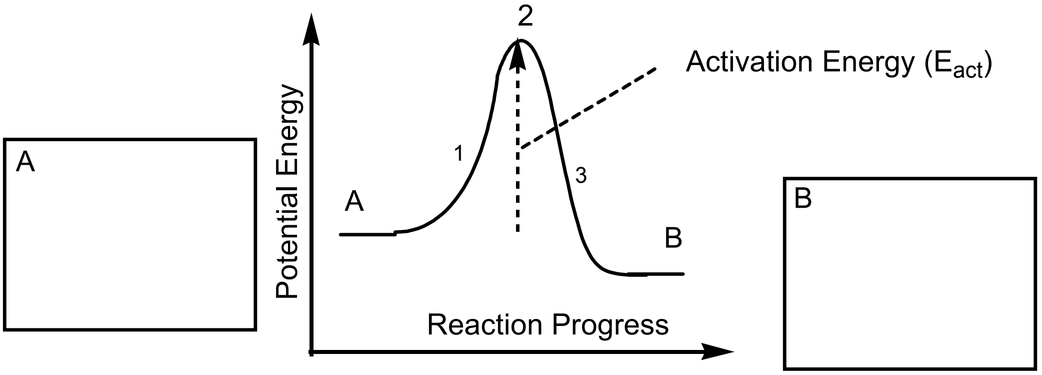
    One such reaction is diagramed below:

    (1) Add enough potential energy to break the double bond (E_{act}),

    (2) free rotation occurs at high energy transition state, then

    (3) reforming the double bond as a mixture of Z and E.

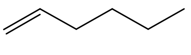
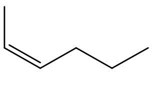
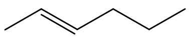
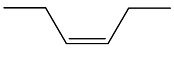
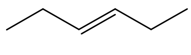
    Draw *E*-2-butene in one box and *Z*-2-butene in the other box, and explain your reasoning.



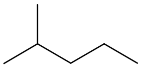
23. Make up an example (not appearing in this ChemActivity) of a pair of molecules that are a) constitutional isomers, b) conformers, c) configurational stereoisomers.

24. Explain why, in the question at the start of Part B of this ChemActivity there is a slash (/) between the words conformers/same.

25. Exercise 9 in Part B asks you to draw all possible isomers (constitutional isomers and configurational stereoisomers) with molecular formula C_6H_{12}. A good way to go about answering such a problem is to start by drawing all possible six-carbon backbones that can accommodate either a ring or a double bond. Then for each unique backbone without a ring, draw all possible ways to accommodate a double bond. For example, a six-carbon straight chain can accommodate a double bond in the five ways shown below.

Draw the five constitutional isomers with molecular formula C_6H_{12} that utilize the backbone at right. (Hint: Look for *E/Z* stereoisomers.)



26. Read the assigned pages in the text, and do the assigned problems.

The Big Picture

The main purpose of Part A is to begin improving your ability to think in three dimensions. 3D thinking is a central skill in organic chemistry. Some people are instantly good at it, but everyone can get good at it with practice (so don't get too frustrated if your group mates seem much faster than you at first). **THE KEY IS WORKING WITH YOUR MODEL SET! You must train your brain to see the representations on the page as 3D objects.**

Parts B and C are designed to start you thinking about same and different. This course will require you to recognize subtle differences between molecules, especially in the context of multiple-choice questions. To understand the topics around the corner you have to train yourself in this skill.

In a subsequent activity we will break down the term configurational stereoisomers into finer categories, so it is critical that you are comfortable with the distinction between conformers, constitutional isomers, and configurational stereoisomers before you move on.

The terms *Z/cis* and *E/trans* can be mystifying until you work with some models. These terms **cis** and **trans** will be applied to a totally new context in the next activity. Watch for this.

If you do not have a model set, you must borrow or purchase one immediately. Next week it will be too late. This activity and the next one are two of several key activities that absolutely require a model set.

Common Points of Confusion

- Each semester a few students come to my office ready to throw in the towel on account of Newman projections. There are a few truly hard concepts in this course, but Newman projections are NOT among them. If you are frustrated by Newman projections you need to sit down with a model set and have someone show you where to put your eye up to a model. In my experience, with this type of coaching **IN THE PRESENCE OF A MODEL SET** everyone eventually "gets" Newman projections.

- **MODELS MODELS MODELS**. In my class I spend lots of energy trying to get students to make models. You might wonder, if they are so helpful, why students need so much encouragement to make them. From talking to students, it seems that many think they can picture a molecule without making the model. Others think models are useful, but not useful enough to justify the five minutes it takes to put a model together. BOTH are WRONG. I have been doing this for a long time, and building a model usually helps *me* see the answer more accurately and *more quickly.* Get in the habit of making a model whenever you are stuck, especially if it has to do with **stereochemistry** ("stereo" meaning "requiring two channels" or "3D").

- The terms **conformational stereoisomer**, **conformer**, **same molecule**, and **identical** are often used synonymously. When chemists say two compounds are the same, picture going to the stockroom, pulling a bottle of each from the shelf, and confirming that the contents of each bottle are the same. Every possible conformation is represented simultaneously in any large sample of a molecule. Only if you freeze the sample toward absolute zero will you begin to see one or a handful of conformations (those at the bottom of the potential energy wells you drew in CTQ 6). Occasionally you will encounter a molecule with groups that are so large that they hinder free rotation of a single bond at room temperature. The bottom line is that, for most molecules, different conformers are just different representations of the same molecule.

- Watch out for "**stereoisomer.**" It is often used in place of "**configurational stereoisomer.**"

- Like Newman projections, *Z/E* configurational stereoisomers drive a few students toward the exit door each semester. And like Newman projections, a few minutes with a model always brings them back. If you are having trouble recognizing *Z* and *E*, **make some models.**

ChemActivity 7: Cycloalkanes

BUILD MODELS: 1,2-DIMETHYLCYCLOPENTANE

PART A: *CIS* AND *TRANS* RINGS

(How can you tell if two groups on a ring are *cis* or *trans* to each other?)

Model 1: 1,2-Dimethylcyclopentane

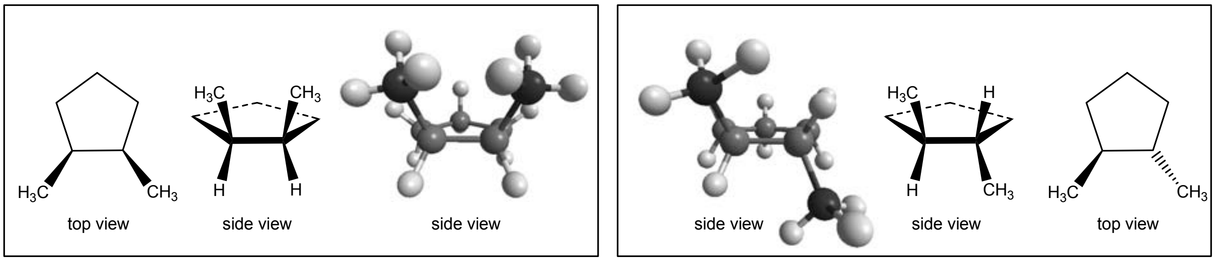


Figure 7.1: Top and Side Views of *Cis* and *Trans*-1,2-dimethylcyclopentane

Critical Thinking Questions

1. Use model(s) of 1,2-dimethylcyclopentane to determine if the molecule in the left box is the same as the molecule in the right box. Recall that…

Two molecules are the same if models of each can be interconverted without breaking bonds.

Memorization Task 7.1: Determining *cis*/*trans* for rings that lie in the plane of the paper

To determine **cis/trans for rings** use the following algorithm: *For two groups on a ring…*

If the groups are attached to the same C, they are **neither** *cis* nor *trans* to one another.

When the ring carbons lie in the plane of the paper (as in the "top views" in Model 1), determine if each group is attached to the ring with a wedge (coming out at you) or dash (going into the paper).

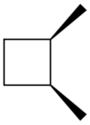
- If both groups lie on the same side of the plane of the paper → groups are *cis* to one another
- If the groups lie on opposite sides of the plane of the paper → groups are *trans* to one another

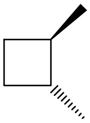
Critical Thinking Questions

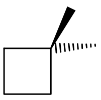
2. In Model 1, label one box "*cis*-1,2-dimethycyclopentane" and the other "*trans*-1,2-dimethylcyclopentane," and state what information is conveyed by each part of the name:

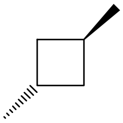
cis 1,2- di methyl cyclo pentane

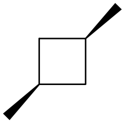
3. Below each structure, write the name of the molecule including *cis* or *trans* if appropriate.









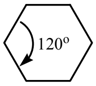


4. Draw wedge and dash skeletal representations of *cis* and *trans* 1,3-dimethylcyclopentane.

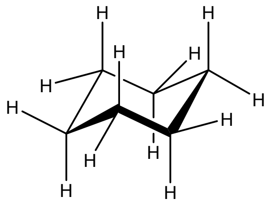
Model 2: Alternate 3-D Representation of a Cyclohexane Ring

Model 1 shows two ways to represent a **cycloalkane** in three dimensions (top and side views). Both of these imply that all the carbons in the ring lie in a single plane. That is, the rings are flat.

In reality, cycloalkanes rarely adopt a flat conformation because lower PE conformations are available. Cyclohexane in a flat conformation would have C—C bond angles of 120° (far from the preferred 109.5°).



The carbons of cyclohexane do NOT form a flat hexagon!



At right is a more realistic representation of cyclohexane → → →
This conformation, called a chair conformation, is the subject of Part B.

Memorization Task 7.2: Determining *cis* and *trans* for rings NOT in the plane of the paper

For two groups on a ring… (*If the groups are attached to the same C, they are neither cis nor trans to one another.*)

If the ring carbons do NOT lie in the plane of the paper, draw a dotted line to define the plane of the ring. (If the ring carbons do not lie in a plane, mark the average—which is usually the horizontal.)

- If bonds to both groups ***point toward*** the same side of this line → groups are *cis* to one another
- If bonds to the groups ***point toward*** opposite sides of this line → groups are *trans* to one another

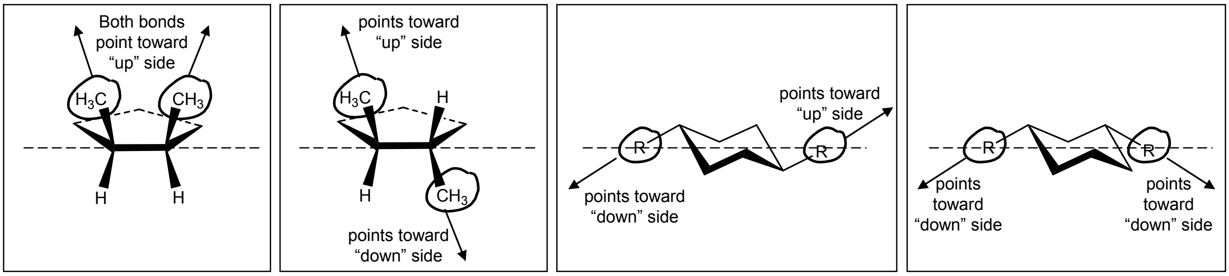
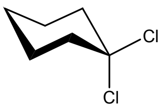

Both bonds point toward "up" side
H_3C
CH_3
H
H
points toward "up" side
H_3C
H
H
CH_3
points toward "down" side
points toward "up" side
R
R
points toward "down" side
R
R
points toward "down" side
points toward "down" side

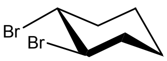
Figure 7.2: Side Views of *Cis* and *Trans* Cyclopentane and Cyclohexane Rings

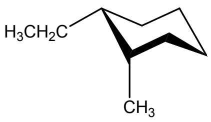
Critical Thinking Questions

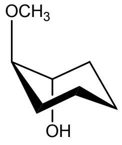
5. Label each ring in Figure 7.2 *cis* or *trans*.

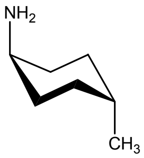
6. Label each of the following disubstituted cyclohexane rings *cis, trans*, or neither.

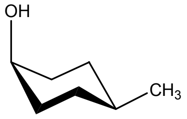












Memorization Task 7.3: Terms and Definitions (*Review from ChemActivity 6*)

- **conformers** = can be interconverted without breaking bonds (i.e., via single bond rotation). Conformers are alternate representations of the same compound (conformers = same molecule).
- **constitutional isomers** = same molecular formula but different *atom connectivity*
- **configurational stereoisomers** = same molecular formula AND the same *atom connectivity*, but are not the same molecule. (**Cannot be interconverted via single bond rotation**!)

Critical Thinking Questions

7. Write the name including **E**, **Z**, **cis** or **trans**, if appropriate, below each molecule.

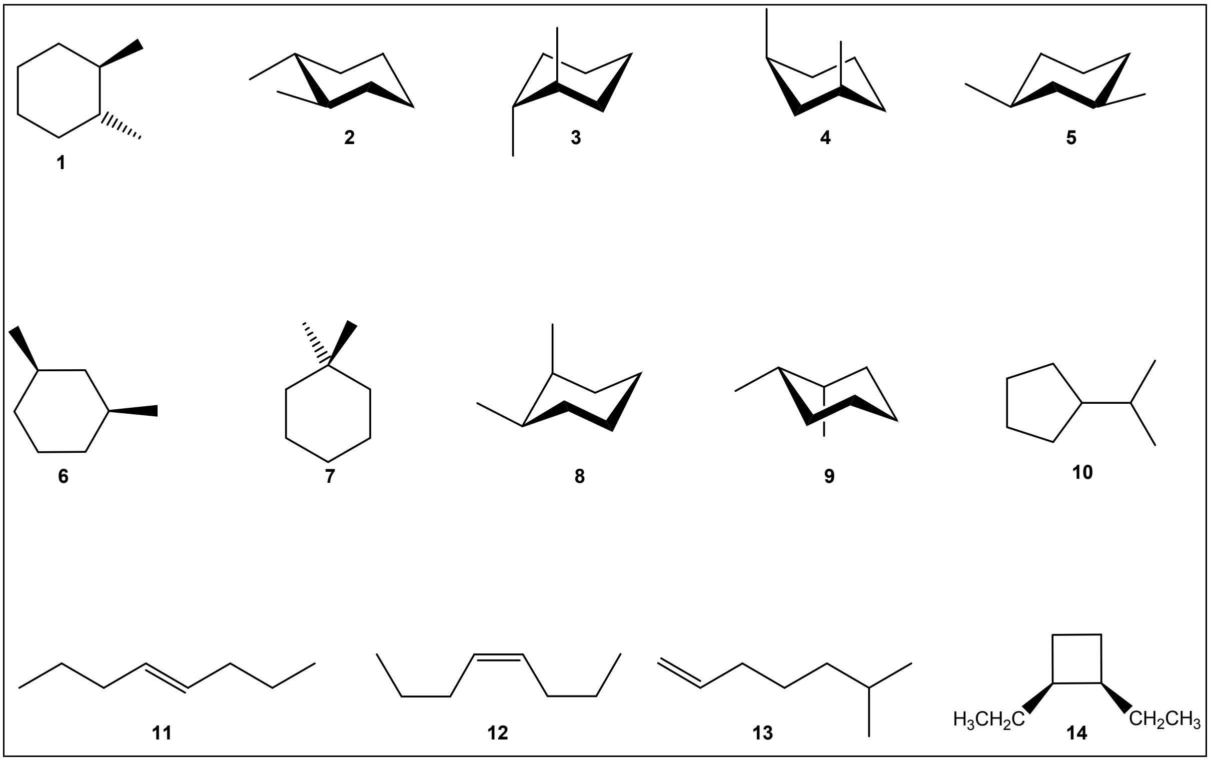
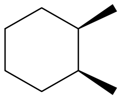


Figure 7.3: Selected eight-carbon cycloalkanes and alkenes

8. Name the molecule at right including *cis* or *trans*, if appropriate. → → →



   a. Label each molecule in Figure 7.3 with its relationship to the structure above ↑
   Choose from: **Conformer (Cf), Constitutional Isomer (CI),** or **Configurational Stereoisomer (CS)**

   b. What was the purpose of asking you to name each of the molecules in Figure 7.3 *before* asking you to identify each one's relationship to *cis*-1,2-dimethylcyclohexane?

BUILD MODELS: CYCLOHEXANE

PART B: CYCLOHEXANE CHAIR CONFORMATION

(If you perform a chair flip on a *cis*-cyclohexane why doesn't it give you a *trans*-cyclohexane?)

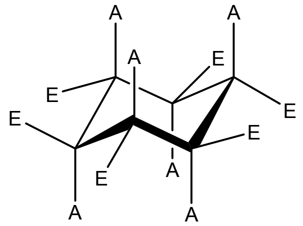
Model 3: Cyclohexane Chair Conformation

Cyclohexane representations like the one at right are called "chairs" because they sort of look like a side view of a fully reclined La-Z-Boy chair.

The chair is the most favorable conformation for **cyclohexane**.

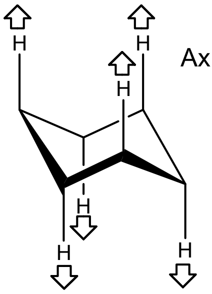
Cyclohexane is the only size ring that adopts a **chair conformation**.

There are two types of positions a group can occupy when it is attached to a cyclohexane chair. These are marked **A** and **E** on the structure at right →



You must be able to make a model of cyclohexane and put it in a chair conformation!!

To do this, focus on the axial H's (those pointing straight up and straight down), and check that…



Axial H's alternate up, down, up, down, etc. around the ring

Bonds to all six axial H's are parallel

If you put the model on a flat surface it rests on a three-legged stand formed by the downward pointing axial H's

Memorization Task 7.4: Groups Attached to a Cyclohexane "Chair"

(A) axial position = attached to a chair via a bond that **points straight up or down** *like an Axis.*

(E) equatorial position = attached to a chair via a bond that **points slightly up or down**
*(On a model you can see that **equator**ial groups point out, toward an imaginary "equator" circling the cyclohexane molecule.)*

Critical Thinking Questions

9. Make a model of cyclohexane in a chair conformation, and explain why the names "axial" and "equatorial" are appropriate.

10. Circle each axial methyl group found on a cyclohexane chair in Figure 7.3 on the previous page.

11. What is the relationship between structures 4 and 5 in Figure 7.3 on the previous page ?

12. Fill in the blanks: *cis*-1,3-Dimethylcyclohexane has two different chair conformations: one with both methyl groups in _________ positions and one with both methyl groups in __________ positions.

Model 4: Ring Strain

Your molecular model set can help predict the best conformation for a molecule because the holes in the atom pieces are consistent with experimentally determined bond angles for sp^3 carbons (109.5°).

It is very difficult to build a model of **cyclopropane**. This is because the 60° bond angles of cyclopropane are very far from an sp^3 carbon's preferred 109.5° bond angles.

Cyclopropane is unstable and high in potential energy. Organic chemists call the extra energy associated with the strained bonds of cyclopropane and other strained rings "**ring strain**."

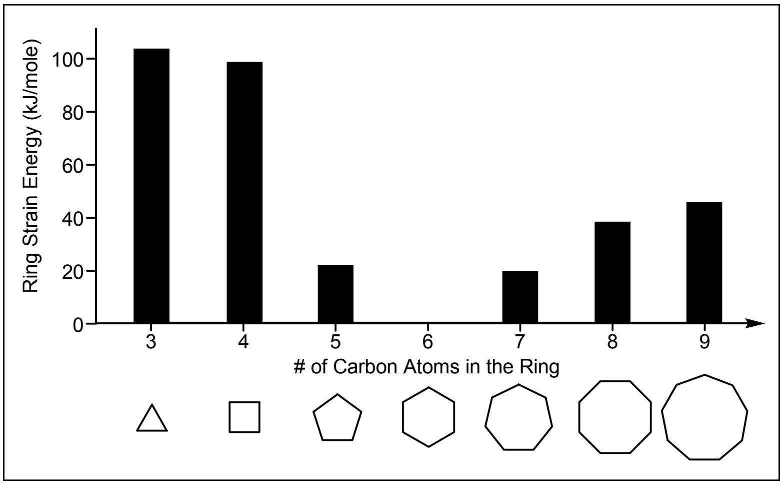
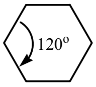


Figure 7.4: Ring Strain as a Function of Ring Size

If cyclohexane were flat (planar) the bond angles would be strained to 120°.



The carbons of cyclohexane do NOT form a flat hexagon!

Instead, **cyclohexane** adopts the zero ring strain **chair conformation** shown below.

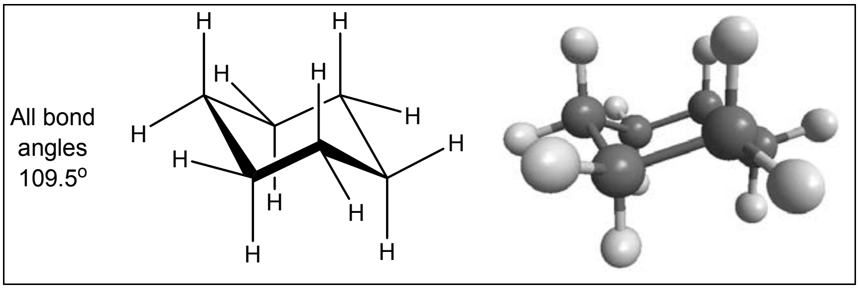


Figure 7.5: Cyclohexane Chair Conformation

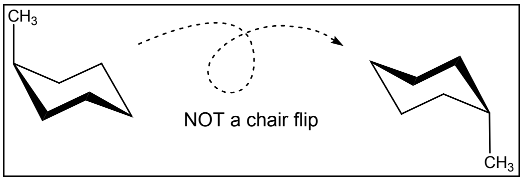
Critical Thinking Questions

13. Circle the **cyclic alkane** in Figure 7.4 that you expect is most commonly found in nature, and explain your reasoning.

Model 5: Chair "Flip"

Let us start by stating what a chair flip is NOT.

It is NOT flipping a model like a pancake →



A **chair flip** is a conformation change in which the "headrest" becomes the "footrest" and vice versa, and **all axial groups become equatorial groups and vice versa.**

The best way to see this with your model is to use a colored ball to mark each axial H. When you successfully perform the chair flip the colored balls will now be in equatorial positions. (*See* Fig. 7.7.)

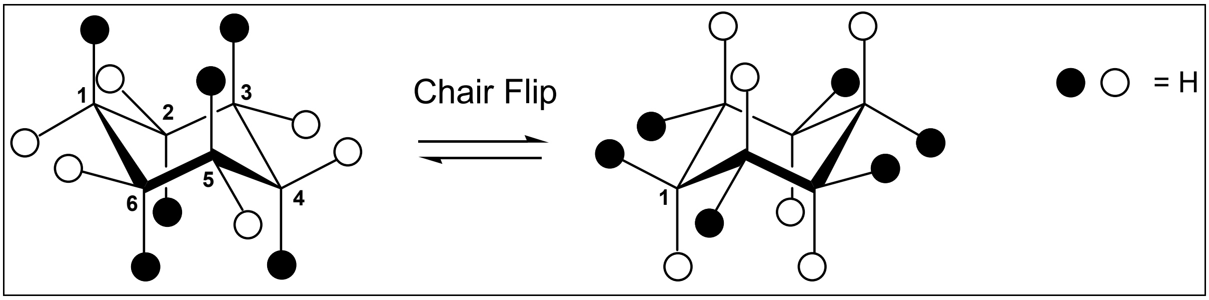


Figure 7.7: Cyclohexane Chair Flip

Critical Thinking Questions

14. Use your model of cyclohexane in a chair conformation to finish numbering the carbons in the ring on the right side of Figure 7.7 (**1** is marked for you).

15. On which structure are the black balls axial, and on which structure are they equatorial?

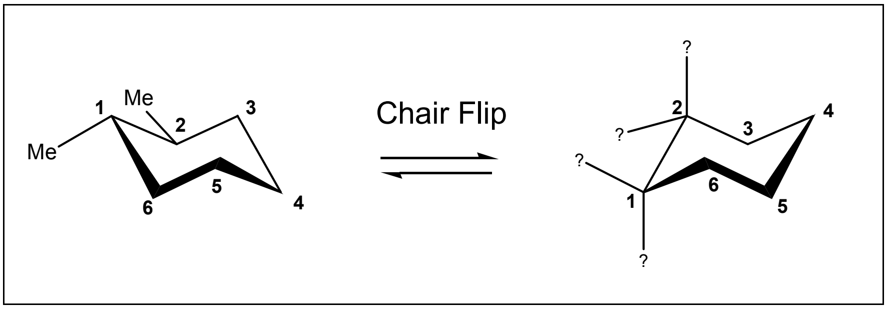
16. Label each black ball on both structures as "up" or "down." ***Hint*:** To determine if an equatorial group is up or down, look at the *axial* group. If the axial group is up, the equatorial group is down.

Memorization Task 7.5: Practice drawing chairs w/ axial groups going in the right direction

The axial group always points straight up or down from the carbon at the bend in the ring. Students often get this wrong when they add an axial H to a skeletal structure (as on the next page).

17. Practice drawing: Draw a representation of *cis*-1,3-dimethylcyclohexane in a chair conformation. Then try to draw the same molecule after a chair flip has occurred.

18. Label each methyl (Me) group on the structure below left as axial or equatorial and up or down. (To determine up/down, it may help to draw in some axial H's.)



a. Label the structure on the left with its name including *cis* or *trans* if necessary.

b. Complete the drawing on the right by replacing each ? with an H or Me to show the correct positions of the methyl groups after a chair flip has occurred.

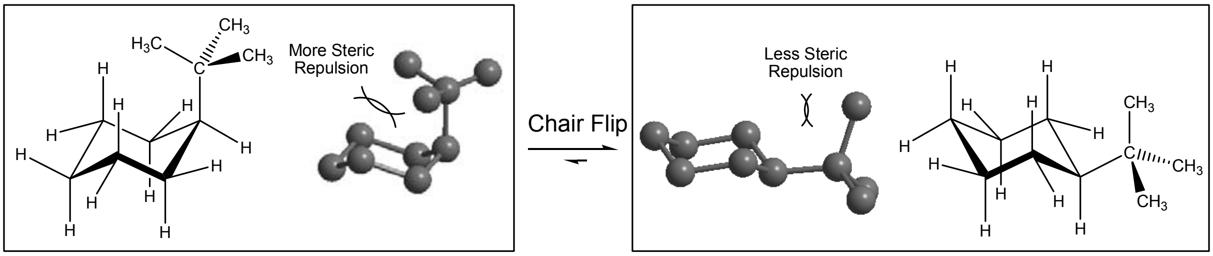
c. Label the structure on the right with its name including *cis* or *trans* if necessary.

d. Are your names for the two structures above consistent with the following facts?

- A *cis* molecule remains *cis*, and a *trans* molecule remains *trans* until a bond is broken.
- No bonds break during a chair flip.

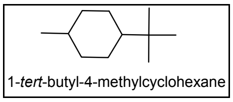
Memorization Task 7.6: It is favorable to put large groups in equatorial positions

A group in an equatorial position points away from the ring where there is more space. A lower potential energy conformation is achieved when large groups are in equatorial (not axial) positions.



Generally the lowest PE conformation has the largest group on the ring in an equatorial position.

Critical Thinking Questions



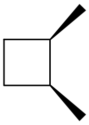
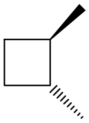
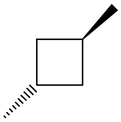
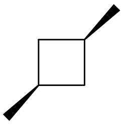
19. Draw **chair representations** of *cis*-1-*tert*-butyl-4-methylcyclohexane and *trans*-1-*tert*-butyl-4-methylcyclohexane in their lowest PE conformations.

20. Which stereoisomer in the previous question is lower in PE? Explain your reasoning.

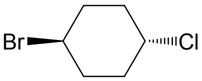
21. Which is lower in PE, structure 4 or 5 in Figure 7.3? Explain your reasoning.

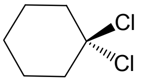
Exercises for Part A

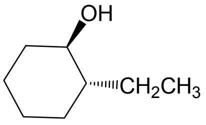
1. A student names the two molecules on the left *cis* and the two molecules on the right *trans* and defends these names by citing that the methyl groups are on the same side for the first two and across from each other for the second two. What misconception does this student appear to hold?

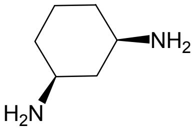





2. Label each of the following as *cis*, *trans* or neither. Below each structure that is *cis* draw a *trans* configurational stereoisomer or vice versa.

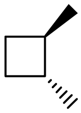








3. Which pair has more in common with one another?



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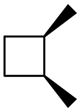

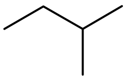

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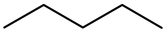
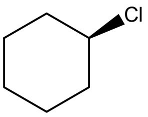
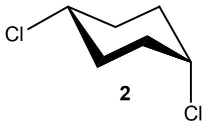


4. What do the pair on the left (above) have in common that the pair on the right does not?

5. What term best describes the relationship between each pair? 1 and 6; 2 and 3; 2 and 4; 4 and 5; 5 and 8; 2 and 7; 8 and 9; 7 and 10; 11 and 12; 11 and 13; 12 and 13; 11 and 2; 11 and 3; 12 and 2; 12 and 3; 7 and 14. (*Choose from identical, conformers, configurational stereoisomers, constitutonal isomers, different molecular formula*)



1



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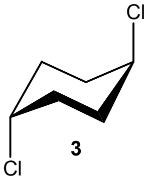

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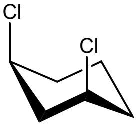

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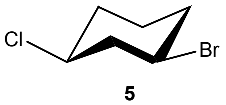

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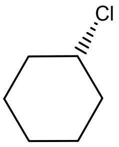

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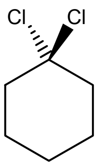

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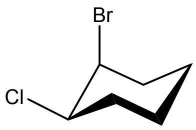

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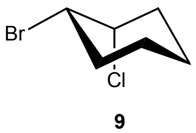

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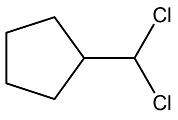

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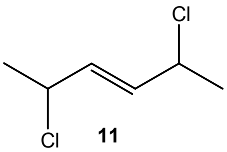

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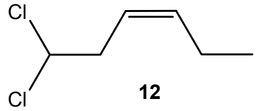

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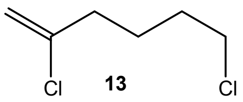

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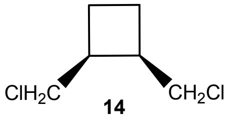


14

6. Check your work by naming each molecule above.

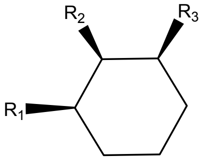
7. Read the assigned pages in your text, and do the assigned problems.

Exercises for Part B

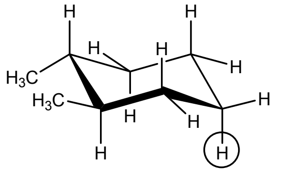
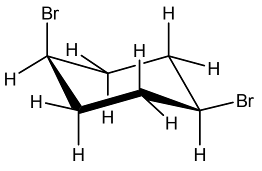
8. Fill in the table by drawing a representation of a *cis* and a *trans* configurational stereoisomer for each row. **Show each molecule in its lowest potential energy chair conformation**.

Generalized name	*cis* configurational stereoisomer	*trans* configurational stereoisomer
1,2-dimethyl-cyclohexane		
1,3-dimethyl-cyclohexane		
1,4-dimethyl-cyclohexane		

9. For each row in the table above, circle the stereoisomer that is lower in potential energy, and explain your reasoning.
10. True or False: If you perform a chair flip on *cis*-1,4-dichlorocyclohexane, the result is *still* called *cis*-1,4-dichlorocyclohexane.
11. Each group on a cyclohexane ring is either axial or equatorial and either up or down.
    a. During a chair flip, only ONE of these changes. Which changes? Which stays the same?
    b. Consider a group that is up and in an axial position on a given cyclohexane ring. Describe this group after a chair flip has occurred.
12. Draw the following molecule in its lowest potential energy chair conformation when…
    a. $R_{1\text{-}3}$ = Me
    b. $R_{1,3}$ = Me, R_2 = *t*-butyl
    c. R_1 = Me, R_2 = Et, R_3 = Pr

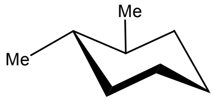


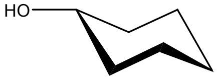
13. Label each molecule drawn below as *cis*, *trans*, or neither.

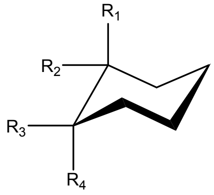
 H H H H H H3C H3C H H H H H  Br H H H H H H H H H Br H H	a. What word is used to describe the type of position held by the circled H in the first drawing. b. DRAW a picture of what the molecule will look like after it has undergone a chair flip. **Do not include any hydrogens in your drawings!**

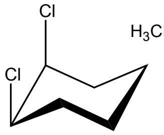
    c. Consider all four drawings (the two above, and the two you drew). For each molecule, circle the conformation, if any, that is lower in potential energy. If it is a tie, circle neither.
    d. Name the two molecules you drew above. Be sure to include *cis* or *trans* in the name, if appropriate.

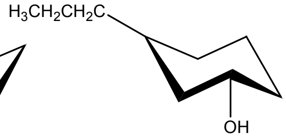
14. What is wrong with each of the following chair representations?











15. The words *cis* and *trans* can be used to name a ring with exactly two nonhydrogen groups. A ring with more than two groups on it cannot be *cis* nor *trans* as a whole, but *cis* and *trans* can be used to specify the relationship between any two specific groups on any ring.

State the relationship (*cis, trans*, or neither) between each pair…

a. X and H_1

b. X and Z

c. Y and Z

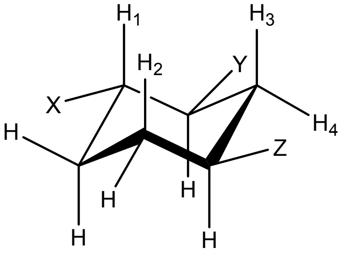
d. H_2 and H_3

e. Z and H_3

f. Z and H_4

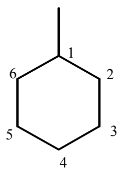
g. Y and H_3

h. H_3 and H_4

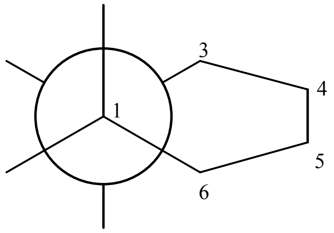


16. Draw *trans*-1- *tert*-butyl-3-methylcyclohexane in its most favorable chair conformation, and explain your reasoning.

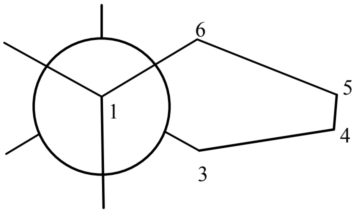
17. Build a model of methylcyclohexane, and use the model to complete the following Newman projections of methylcyclohexane in the chair conformation:



methylcyclohexane



methylcyclohexane
(show CH_3 in axial position)



methylcyclohexane
(show CH_3 in equatorial position)

a. When the methyl group is in an **axial** or **equatorial** (circle one) position, the molecule is in its lowest potential energy conformation.

b. Label one Newman projection above **anti** and the other **gauche** to describe the relationship between the methyl group and C_3 of the ring.

c. In general, which is a lower PE conformation, anti or gauche?

d. Explain how your answer to b and c provide an explanation for why it is more favorable for a large group to be in an equatorial than an axial position.

18. Read the assigned pages in your text, and do the assigned problems.

The Big Picture

In this book, **cyclohexane** is the only ring system whose conformations are studied in detail. This is because it is so common and because the chair conformations of cyclohexane provide a great opportunity to develop our understanding of **cis** vs. **trans**, **conformers** vs. **configurational stereoisomers**, up vs. down, axial vs. equatorial, etc., which will return again and again in future activities. If you do not have a solid grasp of these concepts you will be totally lost going forward.

The best way to improve your understanding of these terms and concepts is to spend some quality time with a model set. By now you are expected to have built up your skill visualizing the 2D representations on the page as 3D objects.

The next activity introduces our first family of organic reactions. We will not have time to make models during class, but your work with models is the key to seeing the 2D structures on the page in 3D.

We will return to working with models during class in ChemActivity 9. So stay in the habit of bringing them with you to class.

Common Points of Confusion

- *Trans* means "across" and *cis* means "same side." The hard part is figuring out across from what or on the same side as what? A common misconception with respect to this is highlighted by Exercise 4.
- Spend some time practicing drawing a cyclohexane chair; then draw the same chair after a flip. Do this with a model in front of you so that you can "program" your brain to see the 3D model when you look at a 2D drawing on the page.
- The key to making a model of or drawing a good chair cyclohexane is to pay close attention to the axial groups. The student who draws an axial group up when it is supposed to be down will lose big points on cyclohexane questions. Remember that each axial group extends straight up or down from the point formed by the ring at each carbon and that axial groups alternate, up, down, up, down, etc., around the ring.
- Many students incorrectly believe that performing a chair flip will change a *cis* cyclohexane into a *trans* cyclohexane or vice versa. Flipping a cyclohexane chair does not break any bonds. As you discovered in Model 1, **you must break bonds to change from *cis* to *trans* or vice versa**.
- Another thing that does NOT change during a chair flip is the general direction of the group ("up" or "down"). A group that is up before a chair flip, will be up after the flip. The same goes for a group that is down.
- It helps some students to focus on what DOES change during a **chair flip**; all **axial positions** become **equatorial positions** and vice versa. The words axial and equatorial refer to conformational relationships, which, like anti and gauche, are constantly changing as the molecule undergoes single-bond rotation at room temperature.

Nomenclature Worksheet 2

INTRODUCTION TO NAMING FUNCTIONAL GROUPS

Model 1: Alkene Nomenclature

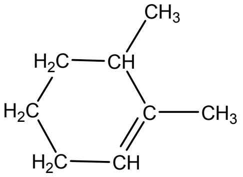
alkene = molecule containing a carbon-carbon double bond (C=C)

Naming an alkene is the same as naming an alkane except the suffix "ane" is replaced with "**ene**" and…

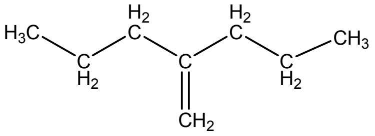
- The parent chain must contain the double bond (unless the parent chain is a ring)
- The parent chain is numbered to give the carbons in the double bond the lowest possible numbers, and the lower of these two numbers is placed before the suffix (e.g., but-1-ene). For a cyclic alkene, this means the double-bond carbons are usually given the numbers "1" and "2."
- For a double bond in a ring, give the double-bond carbon with the most branches the lowest number (usually a "1").
- The endings **diene, triene** and **tetraene** are used to signify **two, three,** or **four** double bonds, respectively. (e.g., buta**ne** becomes buta**diene**; and hexa**ne** becomes hexa**triene**, etc.)

$H_2C{=}CH_2$

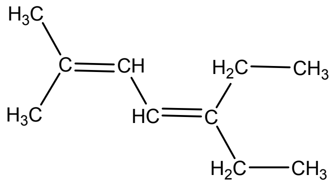
ethene



1,6-dimethylcyclohexene



2-propylpent-1-ene



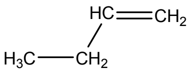
5-ethyl-2-methylhepta-2,4-diene

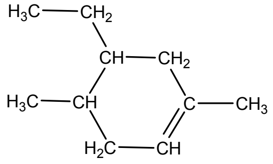
Critical Thinking Questions

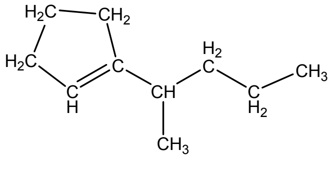
1. A student names the second structure above 2,3-dimethylcyclohex-1-ene. What rule does this violate?

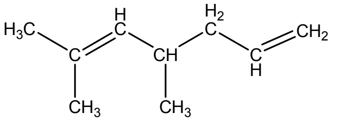
2. In each name in Model 1, circle the number(s) designating the location(s) of the double bond(s).

3. Name each of the following alkenes:









4. Draw the following alkenes:

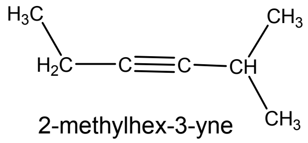
a. 2,3-dimethylbut-2-ene   b. cyclopenta-1,3-diene   c. penta-2,3-diene

Model 2: Alkyne Nomenclature

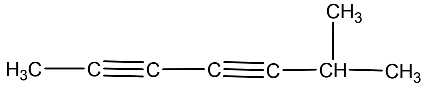
alkyne = molecule containing a carbon-carbon triple bond (C≡C)

$HC\equiv CH$

ethyne

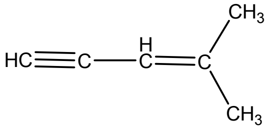


2-methylhex-3-yne



$H_3C-C\equiv C-C\equiv C-\overset{CH_3}{\overset{|}{C}H}-CH_3$

6-methylhepta-2,4-diyne



4-methylpenta-3-en-1-yne

Memorization Task NW2.1: Know the common name of ethyne (HC≡CH) → "acetylene."

Historical Note: IUPAC Name vs. Common Name

Until the last century, chemists had little idea of the structure of chemicals. Consequently, newly discovered chemicals were named at the whim of their discoverers. For example, ethyne can be transformed into vinegar so it was first called **acetylene** after the Latin word for vinegar *acetum*.

Many common names have been incorporated into the official International Union of Pure and Applied Chemistry (IUPAC) naming rules you are learning in this activity. For example, "**but**" (pronounced *beut*), is the IUPAC name for a four-carbon chain. It is derived from the Latin word for butter (*butyrum*) because a four-carbon molecule (butyric acid) is responsible for the smell in rancid butter.

Another example is "**acet**" (from acetylene, HCCH), which is an alternate name for a **two-carbon group**.

Critical Thinking Questions

5. Naming an alkyne is the same as naming an alkene except the suffix "ene" is replaced with what suffix?

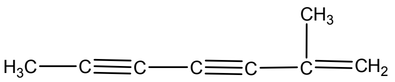
6. Draw the following alkynes:

   a. pent-2-yne

   b. 2,5-dimethylhex-3-yne

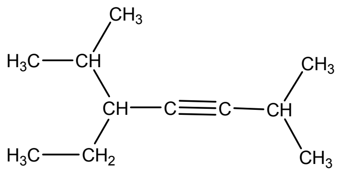
   c. 1-methyl-2-(3-methylbut-1-yn**yl**)cyclohexane
   (Recall that "yl" indicates the name in parentheses is a side chain)

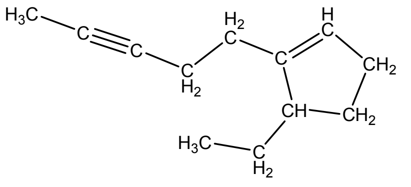
7. Write the IUPAC name for each of the following structures:



$H_3C-C\equiv C-C\equiv C-\overset{CH_3}{\overset{|}{C}}=CH_2$

$H_3C-C\equiv CH$



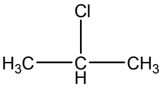


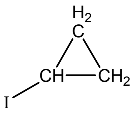
functional group = a site on a molecule where a reaction is likely to occur

Often a functional group contains a heteroatom (N, O, halogen, etc.); however, a double or triple bond is also considered a functional group because, as we will soon see , such bonds are sites of reactivity within a molecule. The following Models contain instructions for naming molecules with various functional groups. These functional groups are also sometimes called **substituents**.

Model 3: Naming Haloalkanes (alkyl halide nomenclature)

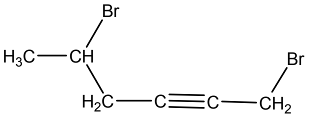
haloalkane = molecule containing a halogen (F, Cl, Br, I)

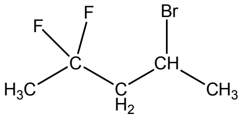

2-chloropropane


iodocyclopropane

CH_2Cl_2

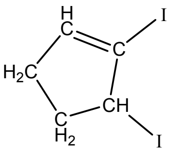
dichloromethane

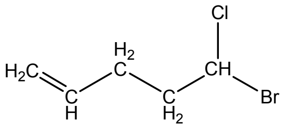

1,5-dibromohex-2-yne

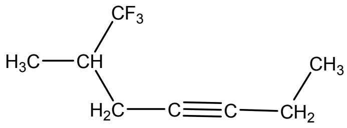

4-bromo-2,2-difluoropentane

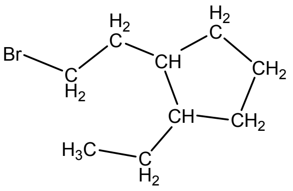
Critical Thinking Questions

8. Based on the examples in Model 3, write the IUPAC name for each structure.



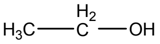




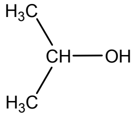


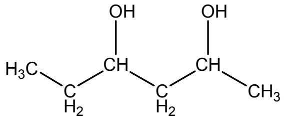
Model 4: Alcohol Nomenclature

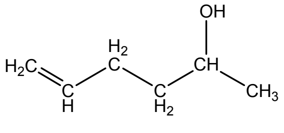
alcohol = molecule containing an OH group

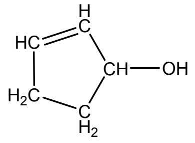

H_3C-CH_2-OH

ethanol


propan-2-ol


hexane-2,4-diol

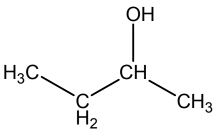

hex-5-en-2-ol

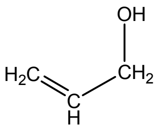

cyclopent-2-enol

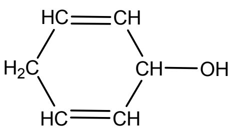
Critical Thinking Questions

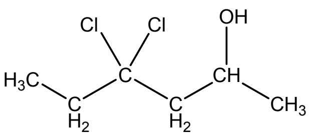
9. Which two structures in Model 4 reflect that fact that OH groups get numbering priority over other functional groups? *(Note that an OH on a ring always gets a "1" so* ***cyclopent-2-en-1-ol*** *is redundant.)*

10. Based on the examples in Model 4, write the IUPAC name for each structure.







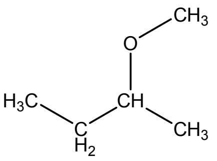


CF_3OH

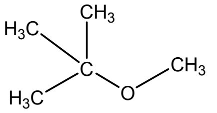
11. Instead of using the ending "**ol,**" an OH can be treated like a substituent or halogen using the term "**hydroxyl.**" For example, hexane-2,4-diol can be called 2,4-dihydroxyhexane. Write an equivalent name for 1,2,3-cyclohexanetriol using the term "hydroxyl."

Model 5: Ether Nomenclature

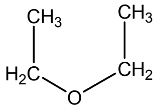
ether = molecule containing R—O—R (where R ≠ H)



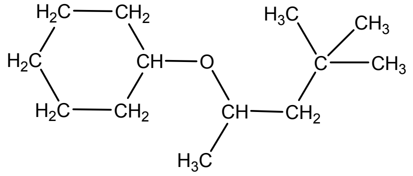
2-methoxybutane



2-methoxy-2-methylpropane



ethoxyethane



(4,4-dimethyl-2-pentanyloxy)cyclohexane

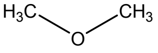
Ethers are named by designating one R group as the parent chain and treating the remaining OR group as a substituent. To indicate the oxygen, the suffix "**oxy**" replaces "**yl**" in the substituent name. For example: meth**yl** becomes meth**oxy**; eth**yl** becomes eth**oxy**, and pro**yl** becomes prop**oxy**, etc.

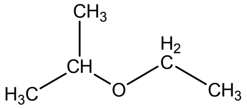
Critical Thinking Questions

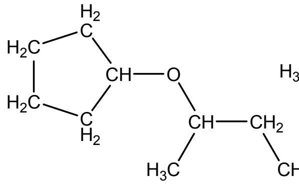
12. Circle the "R" group that is considered the parent chain in each ether in Model 5.

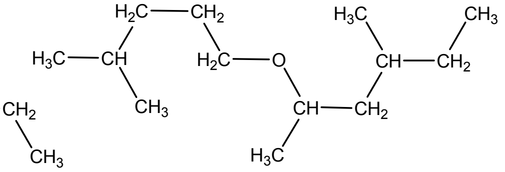
13. Which takes precedence as the parent chain, a ring or non-ring chain?

14. Based on the examples in Model 5, write the IUPAC name for each structure.





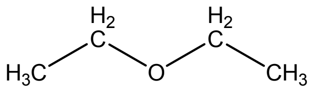




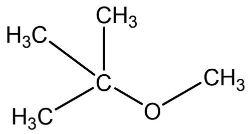
Memorization Task NW2.2: Ether Solvents and an Alternate Way of Naming Simple Ethers

Ethers are polar but do not react with many molecules, so they often are used as solvents.
(A solvent is an inert liquid in which two molecules can be dissolved so they can collide and react.)

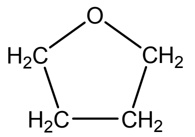
Simple ethers can be named by listing the two alkyl groups followed by the word ether. For example, diethyl ether and methyl *tert*-butyl ether. Be familiar with these names of common ether solvents.



diethyl ether
(ether)



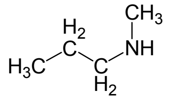
methyl *tert*-butyl ether
(MTBE)



tetrahydrofuran
(THF)

Model 6: Amine Nomenclature

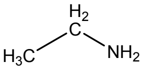
amine = molecule containing NR_3 (where R = H or alkyl)



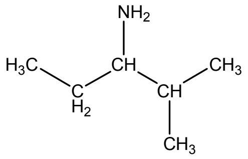
N-methylpropan-1-amine

One way to name an amine (there are many acceptable ways) is to generate a parent name by replacing the last **e** in the corresponding alkane parent name with the suffix "**amine**" (e.g., propane becomes propan**amine**), then inserting a number to indicate the point of attachment to N (e.g., propan-1-amine).

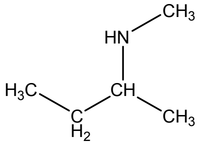
Other alkyl groups attached to N are listed at the front using an *N* (e.g., *N*-methylpropan-1-amine, *above*).



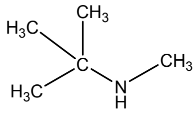
ethanamine



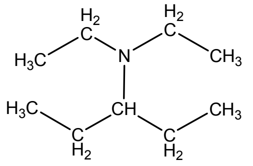
2-methylpentan-3-amine



N-methylbutan-2-amine



N,2-dimethylpropan-2-amine



N,*N*-diethylpentan-3-amine

Critical Thinking Questions

15. Simple amines can be named by turning one alkyl group into the parent name and listing other alkyl groups attached to N at the front, as in ethylamine, triethylamine, or methyl ethylamine. Draw each of these simple amines.

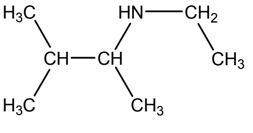
16. (E) Circle the parent chain in each molecule in Model 6.

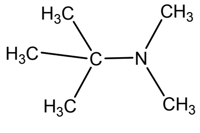
17. (E) What information about the structure does the "3" in 2-methylpentan-**3**-amine convey?

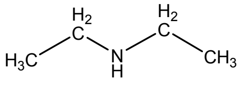
18. (E) Put a box around each alkyl group (other than the parent chain) that is attached to each N.

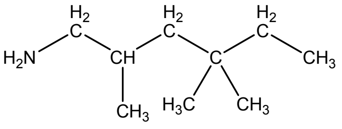
19. (E) What information does the *italicized* capital *N* convey in the name of an amine?

20. Based on the examples in Model 6, write an IUPAC name for each structure.

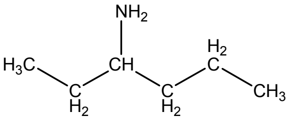


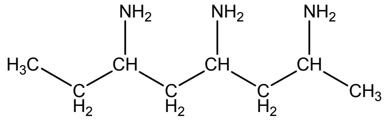


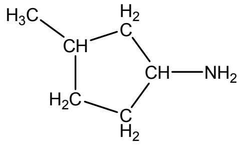


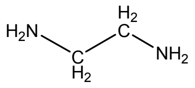


21. Amines containing NH_2 (especially diamines, triamines, etc.) can be named by calling each NH_2 an **amino** group. For example the first two molecules in Model 6 can be named **aminoethane**, and **3-amino-2-methylpropane**, respectively. Name the following molecules using the word **amino**.







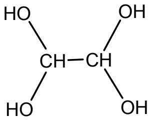
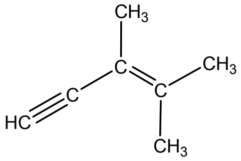
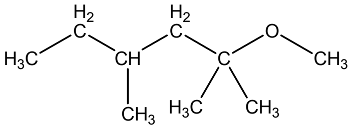
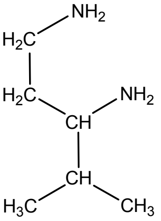
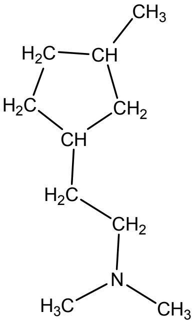
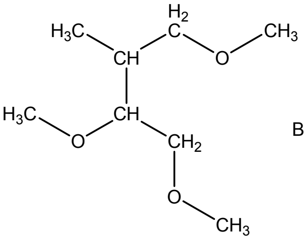
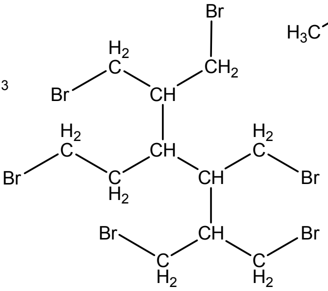
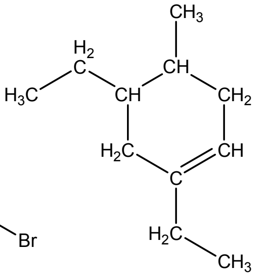


Exercises

1. Draw the following molecules:

   a. 2-methylhept-2-ene
   b. 5-butyl-6-isopropyldec-5-ene
   c. 1-butylcyclopent-1-ene
   d. but-3-enylcyclopentane
   e. (2-methylprop-1-enyl)cyclohexane
   f. nona-1,8-diene
   g. non-4-yne
   h. octa-1,3,5,7-tetrayne
   i. 2,2-dibromo-6-methylheptane
   j. 2-bromo-4-ethyl-2-methyloctane
   k. 1-chloro-2-(chloromethyl)cyclohexane
   l. 4-(1-fluoropropan-2-yl)heptane
   m. 3-propylhexan-2-ol
   n. 3-isopropylpentane-1,4-diol
   o. 1,1,1-trifluoropentan-2-ol
   p. cyclohexa-2,4-dienol
   q. 2-propoxypentane
   r. diisopropyl ether
   s. 1-*sec*-butoxyhexane
   t. 2-methyl-1-propoxyprop-1-ene
   u. octan-1-amine
   v. *N*-methylbutan-1-amine
   w. *N*,3,4-trimethylhexan-2-amine
   x. 1,1-diamino-2-methylpropane
   y. 6-amino-5-chlorocyclohex-2-enol
   z. 3-amino-2,2-dimethylpentane

2. Write an IUPAC name for each of the following structures:

ChemActivity 8: Addition via Carbocation

PART A: ADDITION OF H—X TO A π BOND

(What is the mechanism of the addition of HBr to an alkene?)

Model 1: Carbocation Stability

Recall that a **carbocation** is a cation with a +1 formal charge on a carbon (the **carbocation carbon**). The **carbocation carbon** lacks an octet. This is unfavorable and drives up its potential energy.

An adjacent **electron-donating group** will help complete the octet of a carbocation carbon by donating some electron density to its electron-deficient neighbor.

Memorization Task 8.1: Alkyl groups (e.g., CH_3) are more electron-donating than H

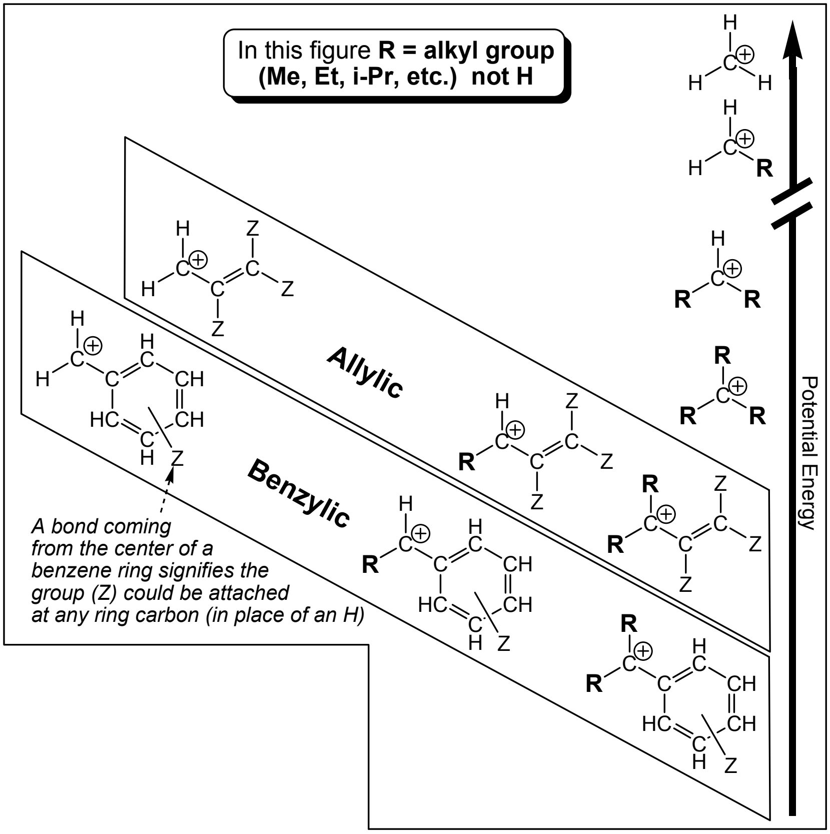
In a later activity we will discuss an argument for why alkyl groups are more electron-donating than hydrogens.

Critical Thinking Questions

1. Which carbocation carbon in Figure 8.1 is farthest from having an octet? Explain your reasoning.

2. Is your answer to the previous CTQ consistent with the fact that highest PE/least stable carbocation in Fig. 8.1 is at the top?

3. What structural feature(s) do the boxed carbocations in Figure 8.1 have that the others do not?



In this figure **R = alkyl group (Me, Et, i-Pr, etc.) not H**

A bond coming from the center of a benzene ring signifies the group (Z) could be attached at any ring carbon (in place of an H)

Figure 8.1: Relative Carbocation Stabilities

4. What extra stabilization do carbocations inside the boxes experience?

5. Explain why **benzylic carbocations** are more stable than **allylic carbocations**.

6. Explain the order of stability within the category “allylic” (or benzylic).

Memorization Task 8.2: Types of Carbocations

Carbocations are categorized according to the number of alkyl (R) and H groups attached to the **carbocation** carbon AND their proximity to π bonds. (*In Figure 8.1 and below, assume $R \neq H$)*

- **tertiary (3°)** carbocation → **three** R groups attached to C (**zero H's** attached to C)
- **secondary (2°)** carbocation → **two** R groups (**one H**)
- **primary (1°)** carbocation → **one** R group (**two H's**)
- **methyl (0°)** carbocation → **zero** R groups (**three H's**)

Appropriate proximity to π bond(s) leads to two special categories of resonance-stabilized carbocations:

- **benzylic** carbocation → + charge next to benzene ring (and in resonance with benzene π bonds)
- **allylic** carbocation → + charge next to (and in resonance with) π bond(s) (not benzene ring)

Critical Thinking Questions

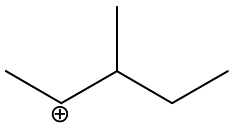
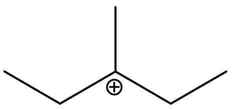
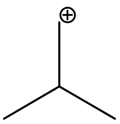
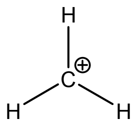
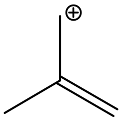
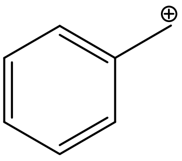
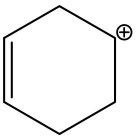
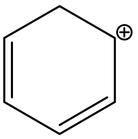
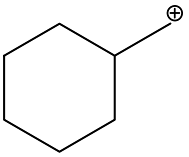
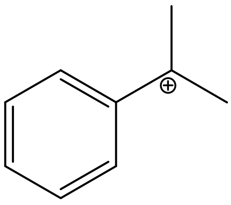
7. Label each carbocation in Figure 8.1 with **3°**, **2°**, **1°**, or **0°**, as appropriate.

8. More than one name can simultaneously apply to a given carbocation. For example, a "tertiary allylic carbocation." Find and label the **tertiary allylic carbocation** in Figure 8.1.

9. It turns out that **methyl carbocations** and **ordinary (non-resonance-stabilized) primary carbocations** are so high in PE and so unstable that they are essentially never observed. Cross out these two carbocations in Figure 8.1, and write **DO NOT FORM** next to them.

Memorization Task 8.3: Assume methyl and *ordinary* primary carbocations do not form.

10. Label each carbocation with one (or more) of the terms in Memorization Task 8.2.

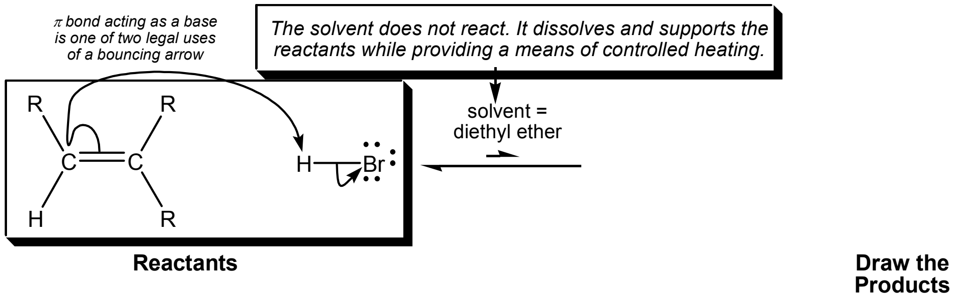











Model 2: (π) Pi Bond Acting as a Base with a Strong Acid (H—X)

The pair of electrons in a π bond can act as a weak base with a strong acid (e.g., HBr, HCl, HI).

We will use a special **curved bouncing arrow** to show which carbon makes a bond to H.

This arrow says… ***The π electrons slide left and make a bond from this carbon to the H (of HBr).***



π bond acting as a base is one of two legal uses of a bouncing arrow

The solvent does not react. It dissolves and supports the reactants while providing a means of controlled heating.

Figure 8.2: π Bond Acting as a Base

Critical Thinking Questions

11. Draw the products that result from the electron movements shown using curved arrows in Fig. 8.2.
12. What type of carbocation is formed in this reaction (3°, 2°, 1°, or 0°)?
13. Draw the products that would result if the arrow "bounced" toward the other carbon.

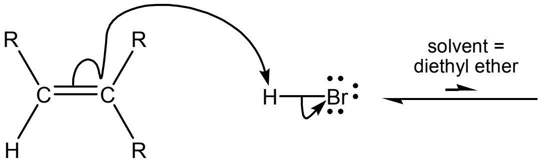
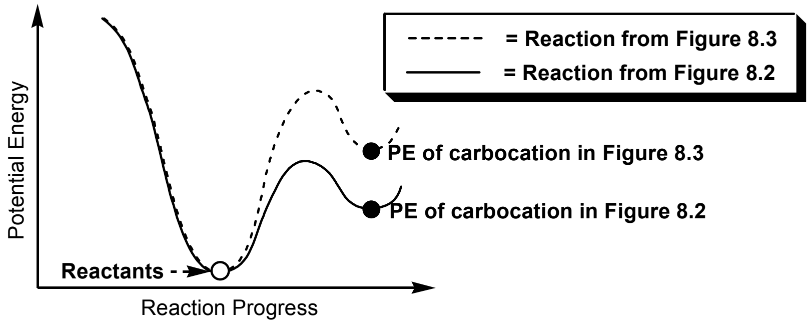


Figure 8.3: Curved arrow bouncing the other way

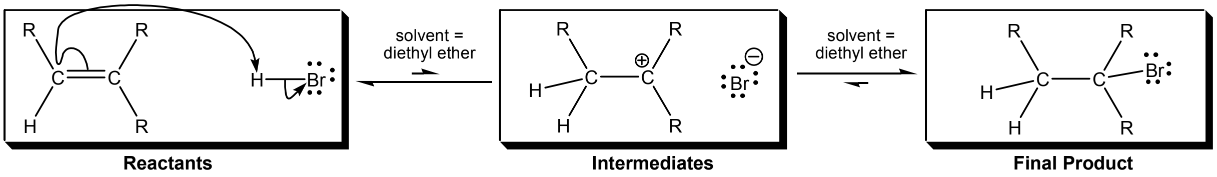
14. Construct an explanation for why the reaction takes place as shown in Figure 8.2 (not Figure 8.3).

15. What information (if any) from the following energy diagram confirms your answer to the previous question?



Model 3: Addition to a π Bond and Markovnikov's Rule

The reaction in Model 2 is the first half of a **two-step** addition reaction, so the products of the first step are called intermediate products or simply "**intermediates**." The last product is the **final product**.



In 1869 Russian chemist Vladimir Markovnikov noticed a pattern in the products of additions to asymmetrical alkenes that has come to be called **Markovnikov's Rule**. It states that…

Markovnikov's Rule:

In addition of HX to a π bond, the X ends up on the carbon with more alkyl (R) groups and fewer H's.

Critical Thinking Questions

16. Add a curved arrow to Model 3 to show bond formation in the second step of the addition reaction.

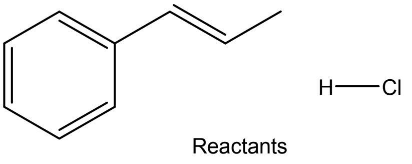
17. Markovnikov did not know why his rule worked. (Carbocations had not been discovered yet.) Complete the following modern restatement of Markovnikov's Rule**:**

In an addition of H—X to a π bond, the X ends up on the carbon that can form the **lower or higher** (circle one) potential energy carbocation.

Memorization Task 8.4: π bonds on a benzene ring do NOT undergo addition.

For reasons we will discuss later, π bonds on a benzene ring are almost always inert (do not react).

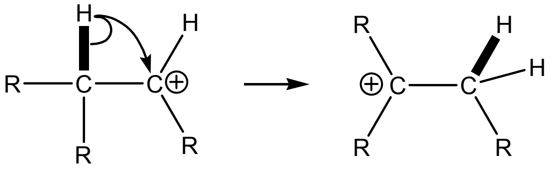
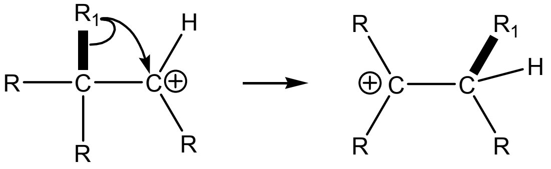
18. The reactants, intermediates, final products, and all curved arrows showing bonds forming and breaking are collectively referred to as the **mechanism** of a reaction**.** For the following reactants:
    a. Explain why the original statement of Markovnikov's rule does not help in this case, but the **modern restatement of Markovnikov's rule** tells you which carbon will get the X (Cl).
    b. Show the mechanism of the most likely addition reaction between the reactants.



Model 4: Carbocation Rearrangements

In a polar solvent, a carbocation can rearrange if the result is a lower potential energy carbocation.
(Rearrangements are the other legal use—besides a π bond acting as a base—for bouncing arrows.)

There are two types: (the electrons that are shifting are highlighted in **bold**)

Hydride (H) Shift	**Alkyl (R) Shift**
 H H R C C⊕ R R R H ⊕C C H R R	 R₁ H R C C⊕ R R R R₁ ⊕C C H R R

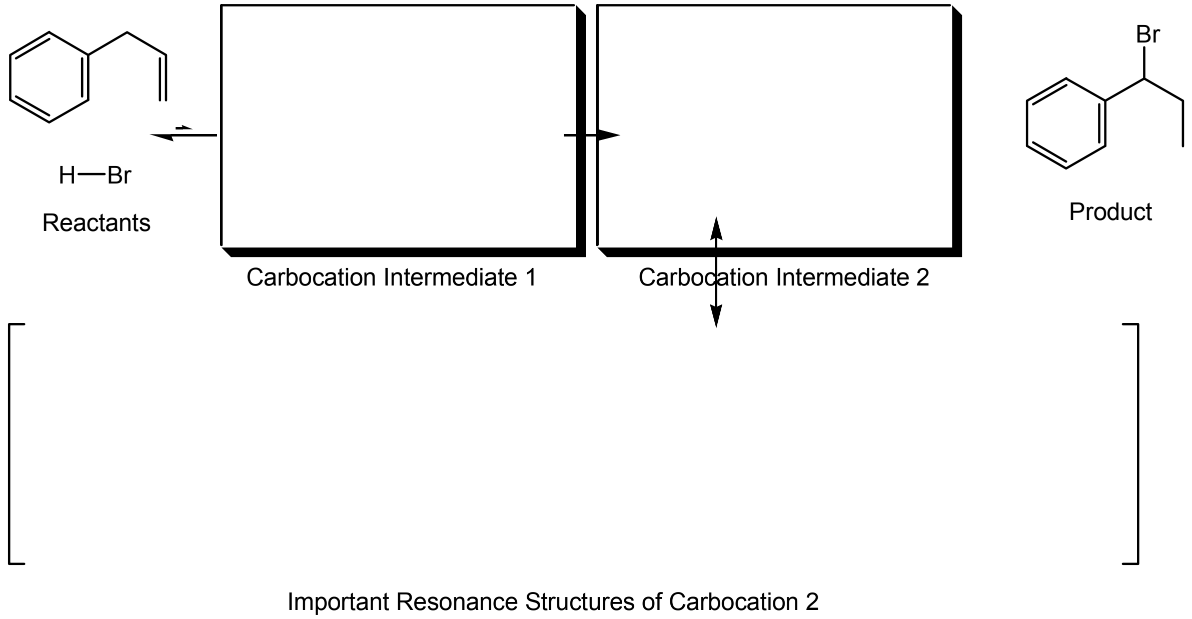
For our purposes, we will assume that an H or R can shift a total of one bond to an adjacent carbon though, given optimal conditions, a variety of exotic carbocation rearrangements can occur.

Critical Thinking Questions

19. For each example in Model 4, explain why the rearrangement shown is downhill in terms of PE.

20. Write a sentence that describes what one of the **curved bouncing arrows** in Model 4 says about the movement of the electrons.

21. Show a mechanism that accounts for the product shown. Include all important resonance structures of carbocation 2. (*Hint*: A rearrangement is part of the mechanism.)


H—Br
Reactants
Carbocation Intermediate 1
Carbocation Intermediate 2
Br
Product
Important Resonance Structures of Carbocation 2

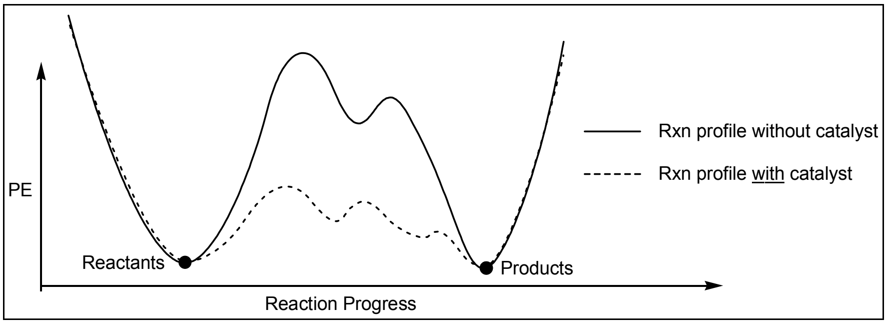
PART B: HYDRATION = ADDITION OF H_2O TO A π BOND

(What is does it mean to say a participant in a reaction is a **catalyst**?)

Model 5: Effect of a Catalyst on a Reaction Profile

A molecule is considered a catalyst in a reaction if both of the following are true:

- The molecule speeds the rate of the reaction by lowering the **activation energy** (E_{act})
- **On net**, the molecule is neither consumed nor produced. (It is often consumed in one step and regenerated in a later step.)



It is a commonly held misconception that a reaction with more steps takes longer.

In fact, ***a reaction's rate is dependent on the height of the highest peak*** *(the largest* E_{act}*).*

Figure 8.4: Typical Effect of a Catalyst on the Progress of a Reaction

Critical Thinking Questions

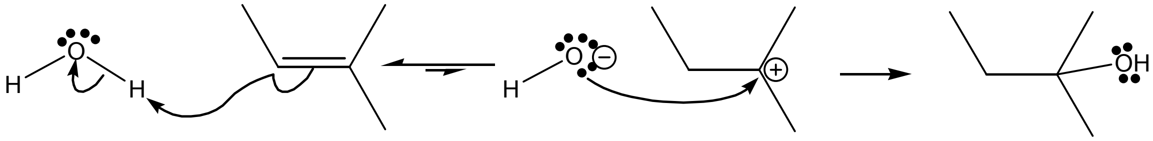
22. The **transition state** is the high-energy point (peak) during one step in a reaction. (One **reaction step** is defined as a change from one local energy minimum through a transition state to another local energy minimum.)
    a. (E) Mark each transition state in Figure 8.4 with a double dagger (‡)
    b. (E) How many steps is each reaction (from Reactants to Products) in Figure 8.4?

23. Explain how you can tell from the energy diagram that the reaction with the catalyst in Fig. 8.4 is faster than the reaction *without* the catalyst.

Memorization Task 8.5: You cannot generate a strong base from a weak base.

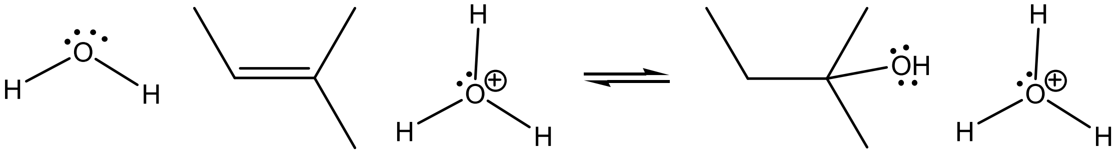
Recall our definition of a strong base: a molecule with a -1 formal charge localized on C, N or O.

24. Explain why the following mechanism for hydration of an alkene **cannot** occur.



Model 6: Acid Catalyst (e.g., H_3O^+)

Hydration of an alkene can take place IF a strong acid (e.g., H_3O^+) is used as a **catalyst**.



You will often see a strong acid catalyst represented as a free H^+, even though H^+ is always bound to some other species, for example,: bound to HSO_4^- in sulfuric acid (H_2SO_4) or bound to H_2O in hydronium ion (H_3O^+).

Critical Thinking Questions

25. In the space below, draw out a possible mechanism for **alkene hydration** shown in Model 6. Hints for getting started can be found in the C**heck Your Work** section below.

Check Your Work:

- The reaction takes three steps.
- The catalyst is consumed in the first step, but regenerated in the last step.
- The π bond is such a weak base that it will react only with a strong acid (not water!!).
- **Hydroxide (HO^-) is NOT involved at any point**.
- ***Any*** lone pair can form a bond to a carbocation (even a lone pair on water).

26. Match your mechanism from the previous question with one of the two reaction profiles (solid or dotted line) on the energy diagram in Model 5, and explain your reasoning. (Check that the other reaction profile in Model 5 matches the mechanism shown at the bottom of the previous page—the one that does not occur.)

Model 7: Electrophiles and Nucleophiles

phile = "lover of" (e.g., audio**phile** = lover of music, biblio**phile** = lover of books)

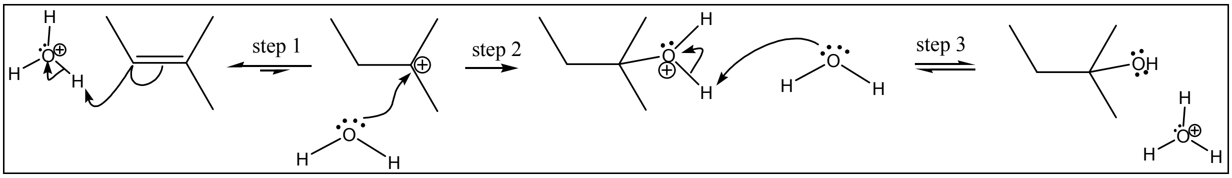
nucleophile = lover of nuclei

electrophile = lover of electrons

Critical Thinking Questions

27. (E) What is the sign of the charge on the nucleus of an atom? (+ or –) (circle one)
28. (E) What is the sign of the charge on an electron? (+ or –) (circle one)
29. (E) A nucleophile is attracted to (+ or –) (circle one) charge.
30. (E) An electrophile is attracted to (+ or –) (circle one) charge.

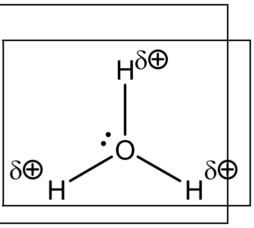
31. This reaction is called "**hydration**" of an alkene because the result is to add H and OH (= H_2O) to the π bond. *(You may want to use this mechanism to check your work on the previous page.)*



a. **H_2O** is acting as a **nucleophile** or **electrophile** (circle one) in Step 2 of the hydration above. Explain your reasoning.

Memorization Task 8.6: Where is the charge on hydronium ion (H_3O^+)?

The +1 formal charge on the oxygen of H_3O^+ is a bit misleading. The electronegativity of oxygen causes it to hog the electrons in all three O—H bonds, leaving a large δ+ charge on each H. This picture of **hydronium ion** → is a more accurate representation of where the + charge is found.



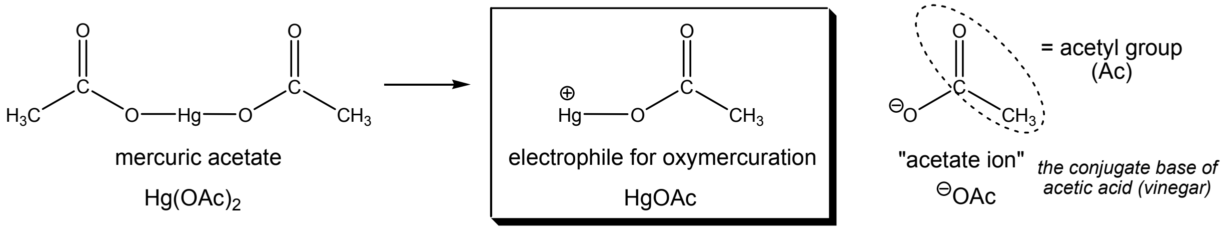
b. **H** of H_3O^+ is acting as a **nucleophile** or **electrophile** (circle one) in Step 1 of the hydration above. Explain your reasoning.

32. The hydration above is one of a family of reactions called **electrophilic addition** reactions. Explain why **electrophilic addition** is an appropriate name for this reaction.

Model 8: Oxymercuration (Useful Hydration of an Alkene)

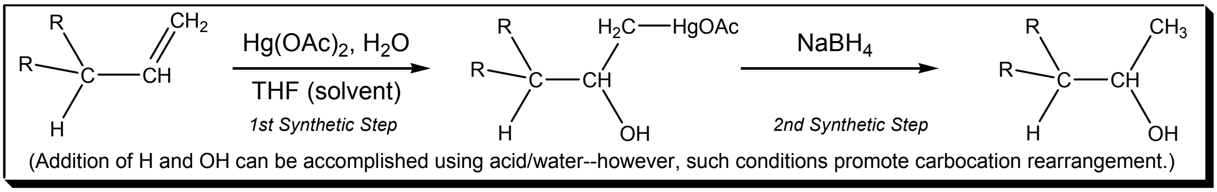
It turns out that the high temperature and acidity required for **acid-catalyzed alkene hydration** causes exotic **carbocation rearrangement**s and makes the reaction impractical for most applications.

Better results are achieved by replacing the electrophile (H^+) with ^+HgOAc (in the box below), which is produced by the decomposition of $Hg(OAc)_2$. "**Ac**" stands for **Ac**etyl group (from **Ac**etic acid= vinegar)



The box below contains the first of many **synthetic transformations** you are **required to memorize**.
Make note cards as we encounter these transformations. Tips for making good note cards can be found in the Exercises.

Synthetic Transformation 8.1: Addition of H and OH (Oxymercuration-Demercuration)



(Addition of H and OH can be accomplished using acid/water--however, such conditions promote carbocation rearrangement.)

The mechanism for the first Synthetic Step above is almost identical to that of acid-catalyzed hydration. THF stands for tetrahydrofuran, an excellent solvent that we will discuss in a later activity. $NaBH_4$ is explored in the Exercises of this activity.

The more you know about a reaction (e.g., the mechanism, the structures of the reagents, the origin of the abbreviations, etc.), the easier it is to memorize.

Memorization Task 8.7: Mechanistic Step vs. Synthetic Step

Mechanistic Step = one step in a mechanism (shown using curved arrows)

Synthetic Step = one step in a recipe that a laboratory chemist would follow.

One **synthetic step** is shown with a straight **reaction arrow** linking the starting and ending molecules. Required **reagents** are often written above or below this arrow (including **solvent** or **temperature**).

Critical Thinking Questions

33. How many synthetic steps are shown in Synthetic Transformation 8.1 above?

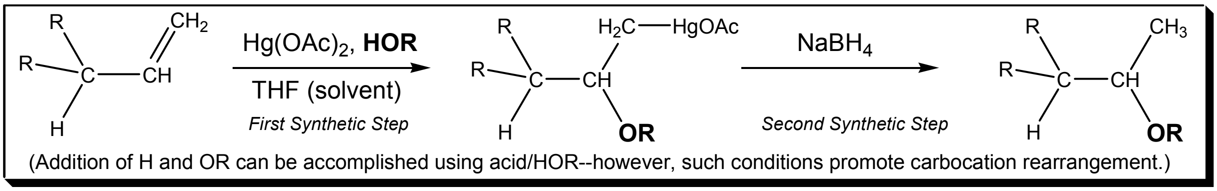
34. Which statement is false?

    a. A mechanistic step may include many synthetic steps.

    b. A synthetic step may include many mechanistic steps.

35. Is oxymercuration-demercuration (the entire process taken as a whole) Markovnikov or anti-Markovnikov? Label Synth. Tranf. 8.1 with one of these terms and explain your reasoning.

Synthetic Transformation 8.2: Addition of H and OR (Alkoxymercuration-Demercuration)



(Addition of H and OR can be accomplished using acid/HOR--however, such conditions promote carbocation rearrangement.)

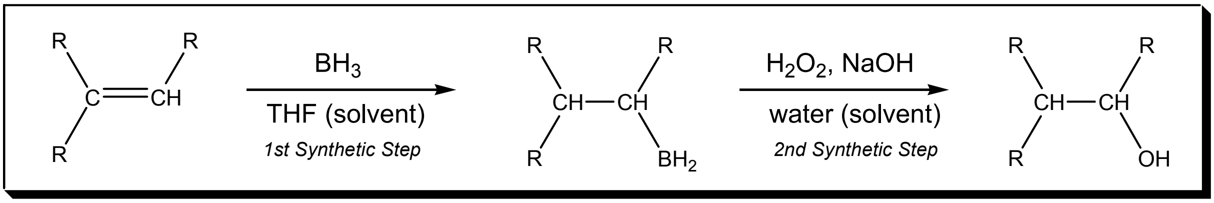
36. What is the difference between oxymercuration and **alkoxymercuration** (*Syn. Tr. 8.1 & 8.2*)?

Memorization Task 8.8: Markovnikov and Anti-Markovnikov Addition of HBr and HOH

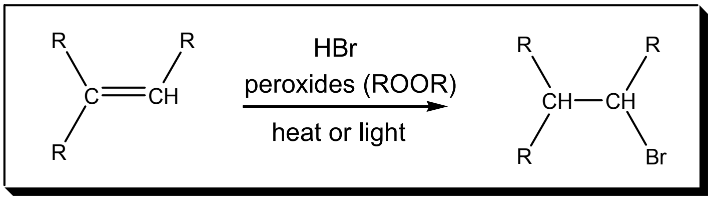
Memorize each Synthetic Transformation in this and all future activities as you encounter them.

It turns out there is a way to add Br or OH to the ***less***-substituted carbon of an alkene. These reactions are called **anti-Markovnikov additions.** We will learn partial mechanisms later, but most students find it helpful to make note cards of both Markovnikov and anti-Markovnikov reactions at this point.

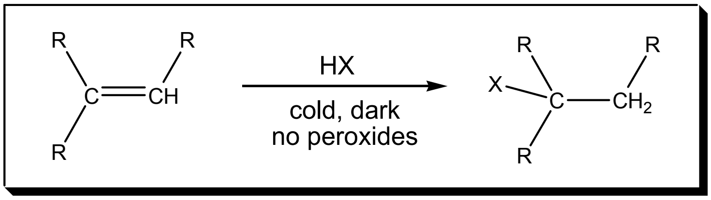
Synthetic Transformation 8.3: Anti-Markovnikov Addition of H and OH



Synthetic Transformation 8.4: Anti-Markovnikov Addition of H and Br



(*from Part A*) Synthetic Transformation 8.5: Markov. Addition of H and X (X = Cl, Br, or I)

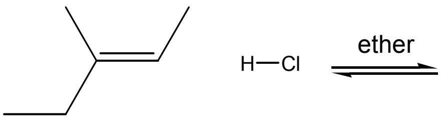


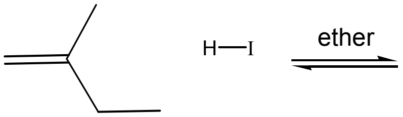
Critical Thinking Questions

37. **Warning:** Students often confuse ***Synthetic Transformation 8.1*** and ***Synthetic Transformation 8.3.*** Take a close look at both reactions, and summarize their similarities and differences.

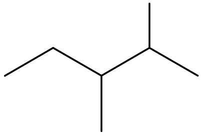
Exercises for Part A

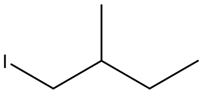
1. Draw the complete mechanism including the intermediate and most likely product for each reaction.





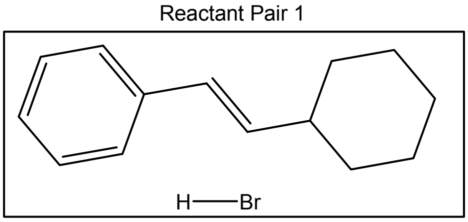
2. Explain why the following products are NOT observed in the reactions above.

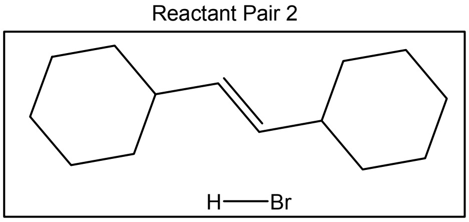




3. Explain why ethene does not react with HX (X = Cl, Br or I) under normal conditions.

4. Draw the complete mechanism of each pair of reactants including any favorable rearrangements and all important resonance structures of all intermediates.



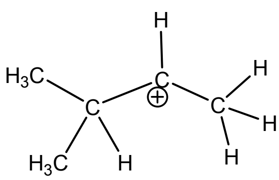


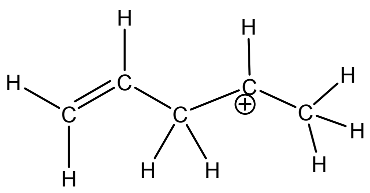
   a. Which reaction has a lower PE carbocation intermediate?

   b. Draw an energy diagram showing the reaction profiles of both reactions in the previous question. Use a dotted line for the first pair of reactants and a solid line for the second pair of reactants. (Assume the energy of the starting materials and products are the same for both pairs and the reactions are neither uphill nor downhill on net.

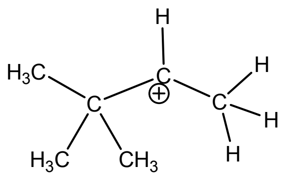
   c. Mark points on the energy diagram corresponding to each carbocation in your mechanisms.

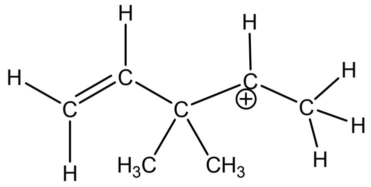
5. Use a curved bouncing arrow to depict the hydride shift that will likely occur for each carbocation below, and **explain why the new carbocation is lower in potential energy** than the original. (Draw any important resonance structures of each!)



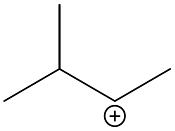


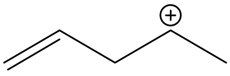
6. Use a curved bouncing arrow to depict the alkyl shift that will likely occur for the carbocation below, and **explain why the new carbocation is lower in potential energy** than the original.

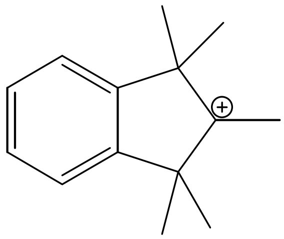


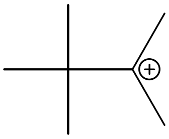


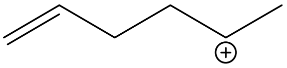
7. Show the carbocation rearrangement (if any) that will occur on each of the following ions. Draw the new carbocation, and briefly describe the driving force for the rearrangement.



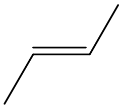


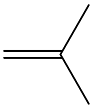


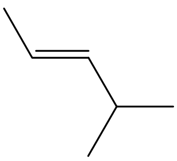


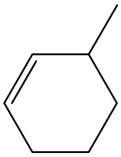


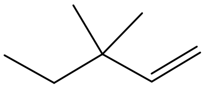
8. For each alkene draw all the likely products of electrophilic addition of one equivalent of strong acid, HX (where X = Cl, Br or I), and use curved arrows to show the mechanism of each reaction. (Some of the reactants are likely to undergo a carbocation rearrangement.)



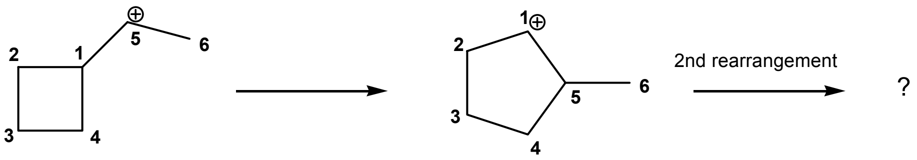








9. Some special cyclic carbocations undergo ring expansion with an alkyl shift (as shown below).

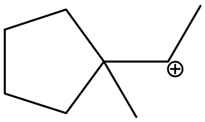


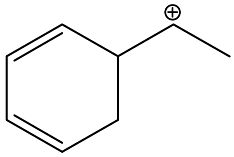
a. Use a curved bouncing arrow to show electron movement in the first carbocation rearrangement above. (Carbons are numbered to assist you.)

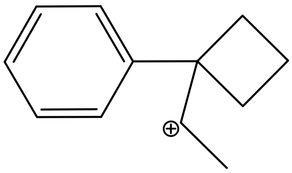
b. Use a curved bouncing arrow to show electron movement in a second carbocation rearrangement that this carbocation is likely to undergo, and draw the resulting carbocation.

c. What is the driving force for each of these rearrangements (It is different for the first rearrangement and the second rearrangement.)?

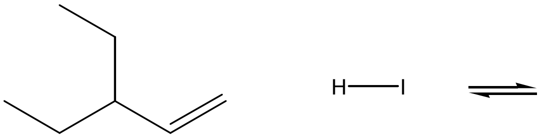
10. Use a curved bouncing arrow to show a likely rearrangement for each of the following carbocations.



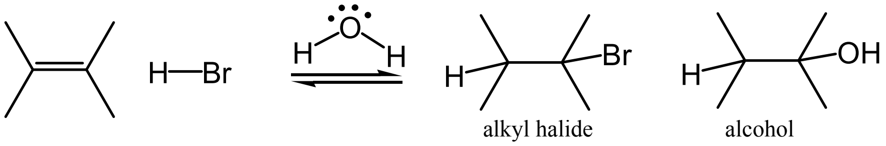




11. The product of the following electrophilic addition reaction, due to symmetry, has two different kinds of H’s. (For those who have done the NMR activity, the proton NMR spectrum consists of only two peak clusters.) Propose a structure for this product, and use curved arrows to show a reasonable mechanism by which it would form.



12. Electrophilic addition in water yields an alcohol product (in addition to the expected alkyl halide.



a. Devise a mechanism for formation of the alcohol product.

b. Draw the product you would expect if the same reaction were run using methanol as the solvent instead of water.

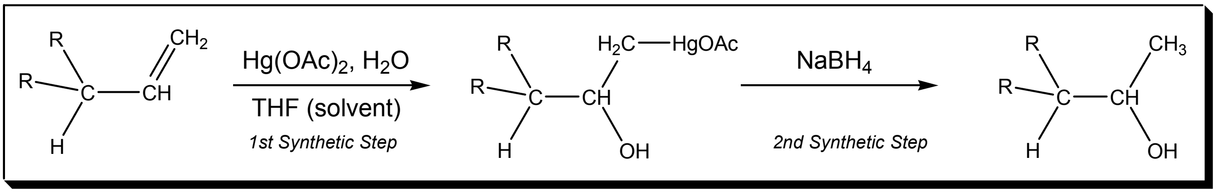
13. Read the assigned pages in the text and do the assigned problems.

Exercises for Part B

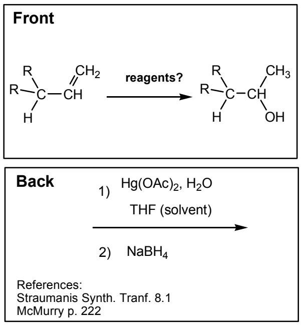
14. Make **four note cards** for each Synthetic Transformation. Use the cards to prepare for…
    (1) questions that give reactants and products and **ask for reagents,**
    (2) questions that give reactants and reagents and **ask for products,**
    (3) questions that give reagents and products and **ask for reactants,**
    (4) questions that test your general **understanding of this reaction**.

For example: Shown below are suggested fronts and backs of cards for Synthetic Transformation 8.1.

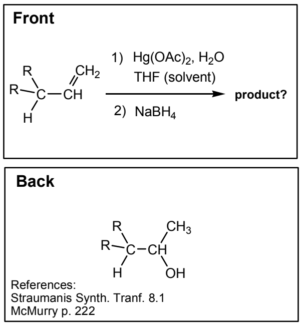
Synthetic Transformation 8.1: Oxymercuration-Demercuration



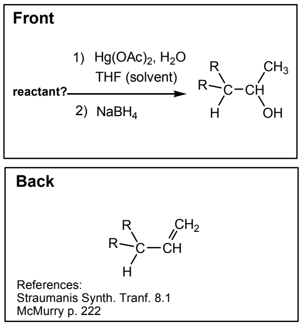
Note Card #1



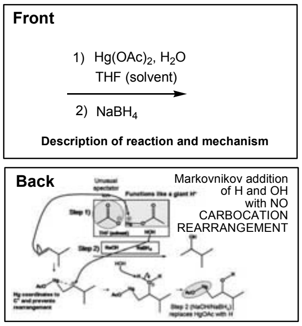
Note Card #2



Note Card #3



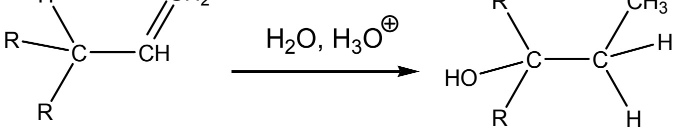
Note Card #4


Front
1) Hg(OAc)2, H2O
THF (solvent)
2) NaBH4
Description of reaction and mechanism
Back
Markovnikov addition of H and OH with NO CARBOCATION REARRANGEMENT

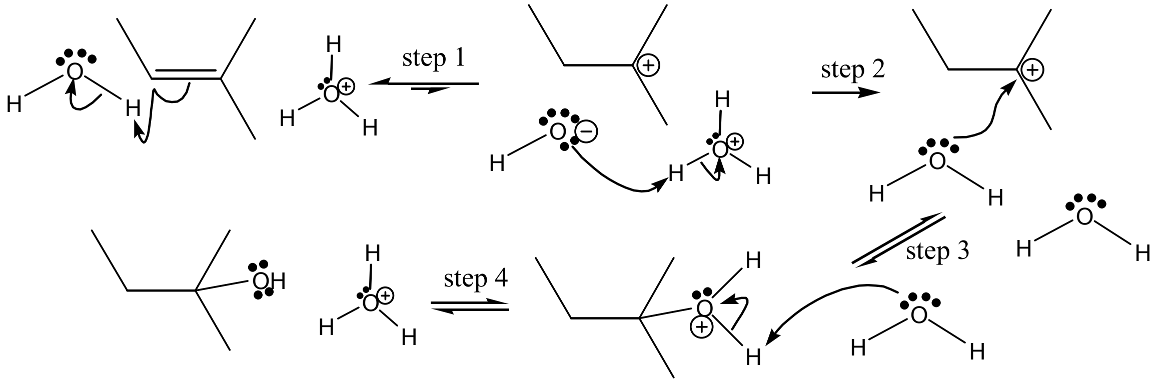
Make note cards for each Synth. Tranf. immediately after the class in which we encounter it!!

If you procrastinate, you will lose points on quizzes and have a huge pile of catch-up work at the end.

15. The more you know about a reaction (i.e., the mechanism, structure of all reactants, etc.), the easier it is to remember.
    a. Show the mechanism for the first synthetic step of Synthetic Transformation 8.1, Oxymercuration. (Note that, instead of H^+, the electrophile in this reaction is ^+HgOAc)
    b. Draw a Lewis structure of $NaBH_4$
    c. The example molecules for oxymercuration and alkoxymercuration in Synth. Tranf. 8.1 and 8.2 were carefully chosen to illustrate what characteristic of these reactions?
    d. Acid-catalyzed hydration of this same molecule results in the following major product. Show a mechanism for formation of this product from the reagents shown.

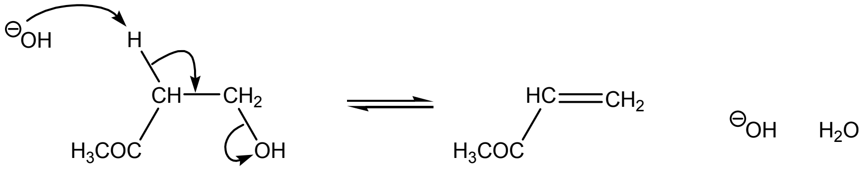


16. A student proposes the following reaction mechanism for the reaction in Model 6. Which step in this mechanism is least favorable? Explain your reasoning.



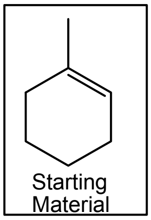
17. Sketch an energy diagram for a reaction that has…
    a. Low-energy reactants, moderate-energy intermediate, and low-energy products.
    b. Low-energy reactants, high-energy intermediate, and low-energy products.
    c. High-energy reactants, and high-energy products.
    d. High-energy reactants, and low-energy products.

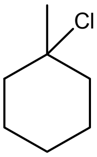
18. The reaction below is an example of a step that produces a high-energy species (hydroxide, HO^-), but is still favorable.

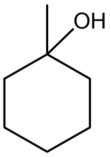


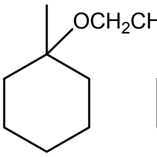
    a. Circle the highest-energy species in the reactants and the highest-energy species in the products, and construct an explanation (based on your current understanding) for why it is not uphill to generate an oxygen with a –1 charge in this case.
    b. Which energy diagram that you drew in the previous question fits this reaction?

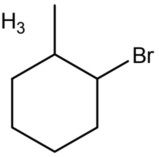
19. Show how to make (synthesize) each of the following molecules from methylcyclohexene.

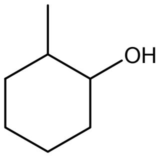

Starting Material











20. Read the assigned pages in the text and do the assigned problems.

The Big Picture

This activity introduces the first few synthetic reactions with some simple synthesis problems in the homework. These synthetic transformations pile up fast. They are the tools in your toolbox for transforming one molecule into another or building a complex molecule from simple starting materials. Synthesis problems bring together a complex set of skills and are often challenging to students, but they are IMPOSSIBLY FRUSTRATING if you have not memorized the tools in the toolbox. Make note cards as directed above, and memorize these reactions as we encounter them.

Common Points of Confusion

- Students sometimes reason that the higher-potential-energy (less stable) carbocation should lead to the major product because a higher-energy carbocation will be more reactive. The flaw in this reasoning is that (though the higher-PE carbocation would produce a more exothermic reaction) it never has a chance to form! The lower-PE carbocation forms preferentially over the higher-PE carbocation, because the lower-PE carbocation takes less energy to make. Since the first step in the reaction has a higher activation energy than the second, the first step is the hard step or slow step (or rate-limiting step).
- Students confuse **oxymercuration**-demercuration (Synthetic Transformation 1) with anti-Markovnikov addition of H and OH (Synthetic Transformation 8.3), perhaps because they both result in delivery of an H and OH to an alkene (though to different carbons!!) or because they both involve boron (but in different steps for different purposes). It is worth your time to put the note cards with these reactions side by side and figure out the differences.

ChemActivity 9: Addition via Cyclic Intermediate

PART A: BROMONIUM ION

(How can we explain the *trans* stereochemistry of some electrophilic addition products?)

Model 1: Electrophilic Addition of Br2

Br—Br is called "**polarizable**" because electrons in the large orbitals that make up the Br—Br bond can slosh back and forth. This makes it easy for the bond to adopt a temporary dipole. Think of waves in a bathtub. At a given moment more water can be at one end of the tub than the other.

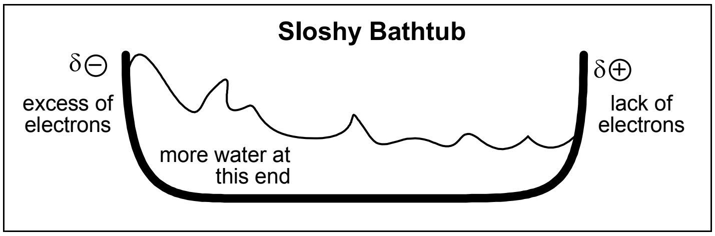


Figure 9.1: Analogy between a sloshy bathtub and a polarizable Br—Br bond

In Figure 9.2 (below) the electrons in Br—Br have "sloshed" to the left, leaving a large partial + charge on one Br atom. At this moment, the π electrons of the alkene can act as a nucleophile and make a bond to the electrophilic $Br^{\delta+}$ atom.

Cl_2 and I_2 also react with alkenes. We focus on Br_2 because Cl_2 reacts too fast, and I_2 reacts too slowly to be useful.

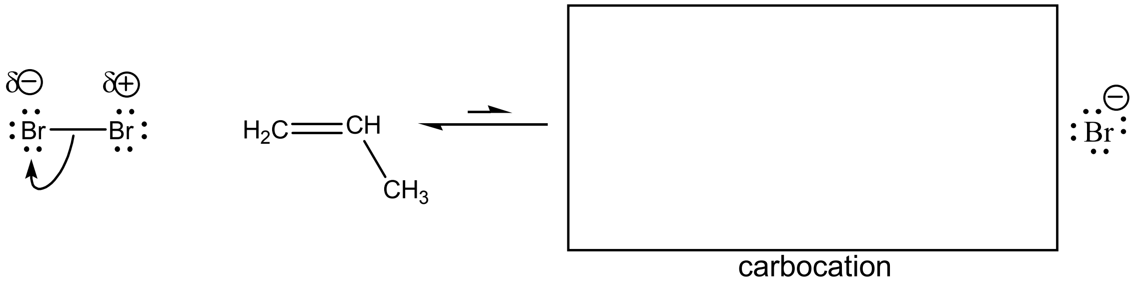
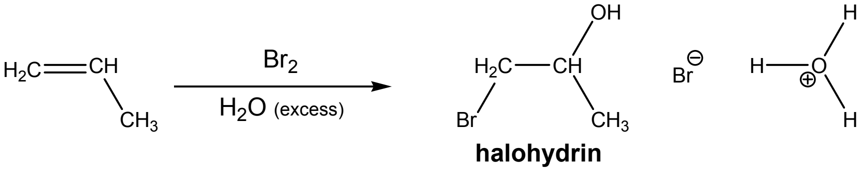


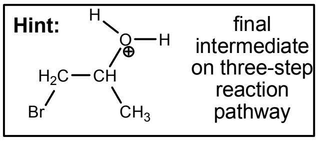
Figure 9.2: Polarized Br—Br serving as an electrophile

Critical Thinking Questions

1. Add a **curved bouncing arrow** to Figure 9.2 showing formation of a likely C—Br bond, and in the box provided, draw the carbocation that is most likely to result from this reaction.
2. The $Br^{\ominus}$ produced by the reaction in Figure 9.2 could combine with the carbocation you drew to give a dibromide product (a product with two Br atoms). Use a curved arrow to show the $Br^{\ominus}$ making a bond to the carbocation, and draw the resulting dibromide product.

3. If the reaction on the previous page is carried out in the presence of a large excess of another nucleophile (e.g., H_2O), this other nucleophile will out-compete Br $^{\ominus}$. Show a possible mechanism (via a carbocation intermediate) for formation of the **halohydrin** shown below. (**halohydrin** = a molecule with a halogen and an OH on adjacent carbons)



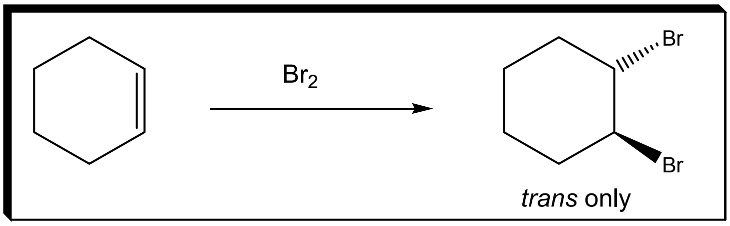


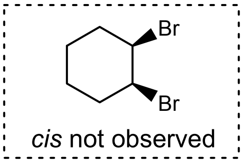
4. Is the reaction above **Markovnikov** or **anti-Markovnikov** (circle one)? Explain your reasoning.

Model 2: Explanation for *Trans*-Only Stereochemistry

When Br_2 is added to a double bond in a ring, the *cis* configurational stereoisomer is not observed.

Synthetic Transformation 9.1: Addition of Br2 to an Alkene



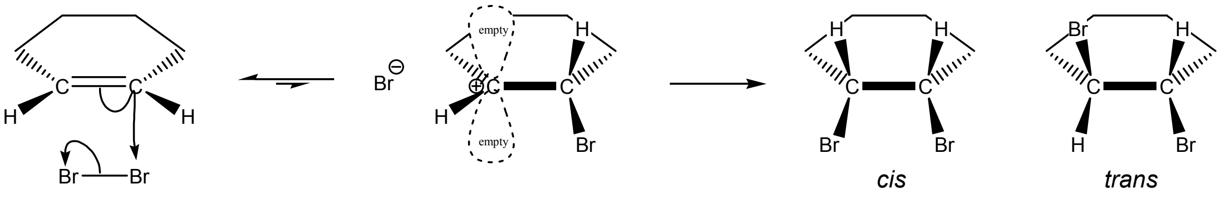


stereoselective = certain configurational stereoisomers (e.g., *trans*) are observed at the expense of others

Critical Thinking Questions

5. The mechanism below CANNOT explain the **stereoselectivity** of this reaction.

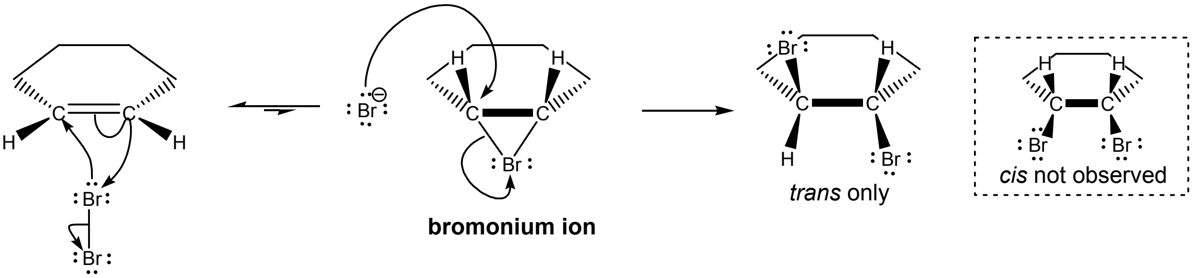
Add two curved arrows showing that the nucleophilic Br $^{\ominus}$ could attack either the top or bottom lobe of the empty *p* orbital of the carbocation, giving both the *cis* and *trans* products.



Model 3: Bromonium Ion

In 1937 chemists Irving Roberts and George Kimball suggested the observed *trans*-only stereochemistry of this reaction could be explained by a three-member ring called a **bromonium ion**.

(Historical note: At about this time, Kimball taught chemistry PhD student and soon-to-be author Isaac Asimov.)



Low-temperature experiments have since confirmed the existence of bromonium ions as the intermediate in electrophilic additions of Br_2 *to alkenes, including additions to* non*cyclic alkenes such as the one in Model 1.*
(Low-temperature experiments were used to slow the decomposition of and to study the normally short-lived bromonium ion.)

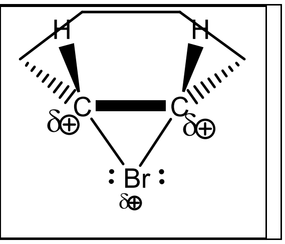
Critical Thinking Questions

6. Construct an explanation for why it is easier for the nucleophilic Br$^{\ominus}$ to make a bond to a carbon **anti to** (on the opposite side from) **the Br involved in the bromonium ring**.
(Such **anti addition** produces exclusively *trans*.)

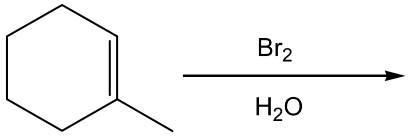
7. The bromonium ion in Model 3 is missing a formal charge (though all lone pairs are shown). Complete the structure by adding the missing formal charge.

Memorization Task 9.1: Where is the charge on a bromonium ion?

Br of a bromonium ion hogs much of the electron density in the C—Br bonds. Like the formal charge on O in H_3O^+, the formal charge on Br is misleading. Much of the + charge on a bromonium ion actually resides on the carbons. This explains why the nucleophile makes a bond to one of the carbons.



8. Draw the **halohydrin** product of the following reaction, and label it **Markov.** or **anti-Markov**.



PART B: EPOXIDES

(How do the products differ if an expoxide is opened using acidic versus basic conditions?)

Model 4: Epoxides

Cyclic ethers are normally quite stable. For example, **THF** (tetrahydrofuran) is commonly used as a **solvent** because it provides a polar medium for carrying out polar reactions without itself reacting.

In contrast, a three-member cyclic ether (e.g., **epoxide**) is highly strained and reactive. Such rings are commonly used in synthesis, because, like bromonium ion rings, they lead to **stereoselective** products.

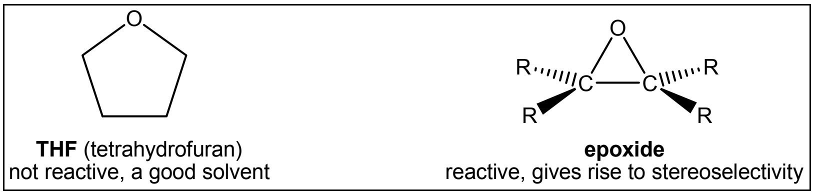
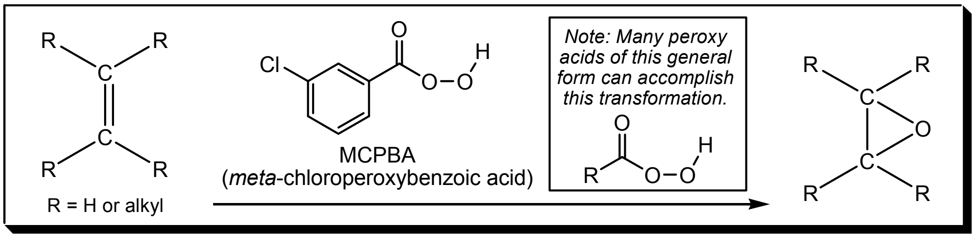
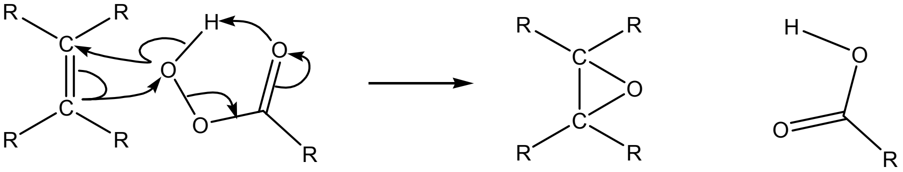

O
THF (tetrahydrofuran)
not reactive, a good solvent
O
R
C
C
R
R
R
epoxide
reactive, gives rise to stereoselectivity

Figure 9.3: Examples of cyclic ethers

Synthetic Transformation 9.2: Oxidation of an Alkene to an Epoxide


R
R
C
C
R
R
R = H or alkyl
Cl
O
O
O
H
MCPBA
(*meta*-chloroperoxybenzoic acid)
Note: Many peroxy acids of this general form can accomplish this transformation.
O
R
O
O
H
R
R
C
O
C
R
R

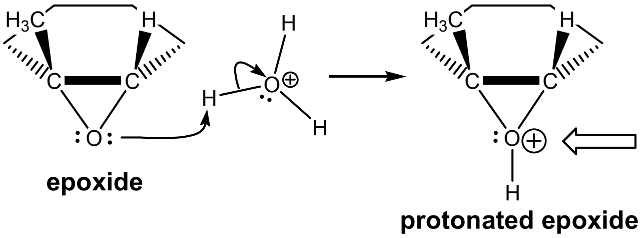
Though the result above is most important, a mechanism is provided below in case it helps you remember the reaction.



Model 5: Acid-Catalyzed Epoxide Ring Opening (Acidic Conditions)

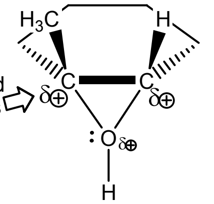
Reaction with an acid is often called “**protonation**” because the function of the acid is to transfer an H^+, and an H atom with no electrons (H^+) is simply a **proton**.

A **protonated epoxide** has almost identical reactivity to a bromonium ion in that both three-member rings, when opened by a nucleophile, give **Markovnikov *trans*** products.



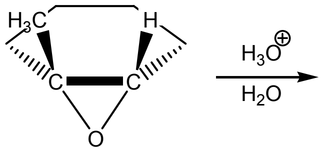
Like bromonium ion, the charge on a protonated epoxide is only formally assigned to the heteroatom (oxygen).

As shown at right, the + charge is in fact distributed to the carbons due to inductive effects.



Critical Thinking Questions

9. Show the mechanism of this reaction. Check your work: The diol product is described by the underlined phrase in Model 5 (**diol** = molecule with two OH groups), and the curved arrows show the first step.



Model 6: Isotopic Labeling

isotopes = two atoms of the same element with different masses (due to a different number of neutrons)

The most abundant isotope usually has no superscript. Other isotopes are labeled with a superscript showing their atomic weight (e.g., ^{13}C). ^{2}H is often represented with a **D**, which stands for **deuterium**.

A heavy isotope can be used in place of the ordinary isotope (e.g., ^{13}C vs. C) to track an atom through a reaction. This practice is called **isotopic labeling**.

In this book we will assume that isotopes have identical reactivities (i.e., D reacts the same way as H).

In fact, a molecule with a heavy isotope usually has a slightly slower reaction rate. This slowing is called an isotope effect.

Table 9.1: Common Isotopes Used for Labeling Organic Molecules

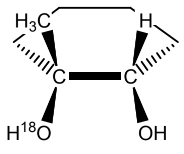
Atom Label	Atomic #	Mass
H	1	1
D (or ^{2}H)	1	2
C	6	12
^{13}C	6	13

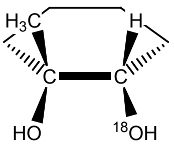
Atom Label	Atomic #	Mass
N	7	14
^{15}N	7	15
O	8	16
^{18}O	8	18

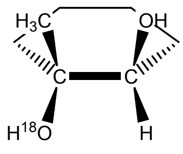
Critical Thinking Questions

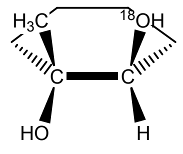
10. (E) How many extra neutrons does a deuterium atom have in comparison to hydrogen atom?

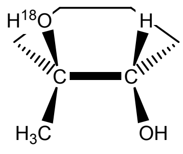
11. If water in the reaction at the top of the page is replaced with ^{18}O-labeled water, which of the following products is expected? Explain your reasoning.

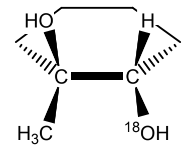












Model 7: Epoxide Ring Opening (Basic Conditions)

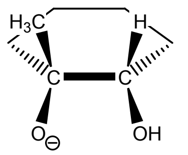
An **epoxide** ring can be opened by a strong base acting as a nucleophile (without its being protonated).

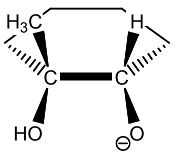
Like other ring openings, this reaction gives ***trans*** products, but the regiochemistry is **anti-Markovnikov**!

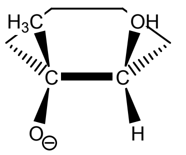
The explanation for this result is that in basic conditions (unlike in acid conditions), there is no positive charge on the carbons, so the nucleophile makes a bond to the less-hindered C. (The C that is easier to get to.)

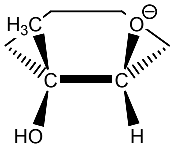
Critical Thinking Questions

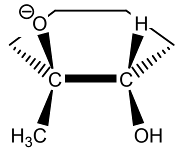
12. Circle the one product that will result from the reaction below (label the product ***cis, trans*****, Markov.** or **anti-Markov**., as appropriate, and draw the mechanism of its formation.

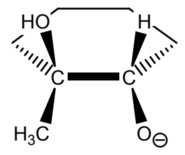


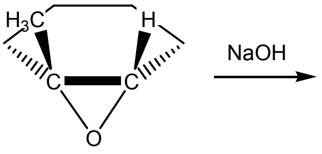




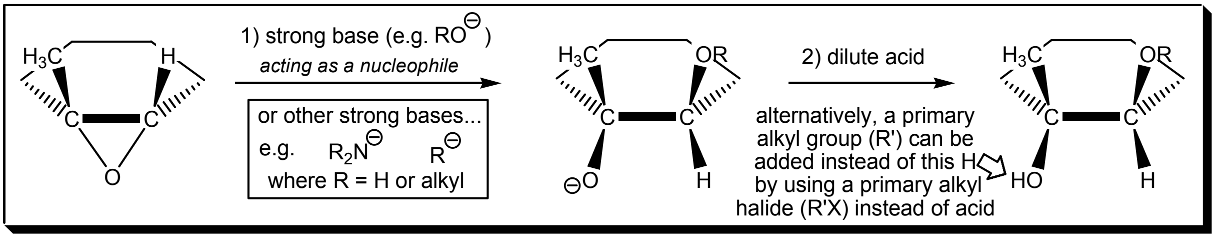








Synthetic Transformation 9.3: anti-Markov. Epoxide Ring Opening (Basic Conditions)



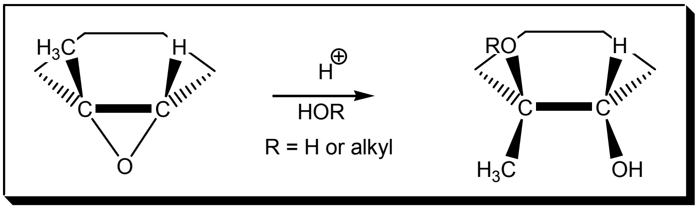
H3C
H
C
C
O
1) strong base (e.g. RO⊖)
acting as a nucleophile
or other strong bases...
e.g. R2N⊖ R⊖
where R = H or alkyl
H3C
OR
C
C
⊖O
H
2) dilute acid
alternatively, a primary alkyl group (R') can be added instead of this H by using a primary alkyl halide (R'X) instead of acid
H3C
OR
C
C
HO
H

13. In a synthetic transformation, reagents that must be added in separate steps are written over different synthetic-step reaction arrows, or given different step numbers, or both.

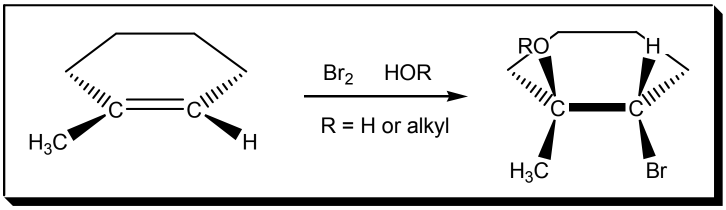
    In Synth. Transf. 9.3 the base is added first and allowed time to react. When reaction with the base is done, an equivalent molar amount of acid is added. What would be the result if both reagents were added at the same time?

Memorization Task 9.2: Make note cards for all Synthetic Transformations ***(more on next page)***

Synthetic Transformation 9.4: Markov. Epoxide Ring Opening (Acidic Conditions)



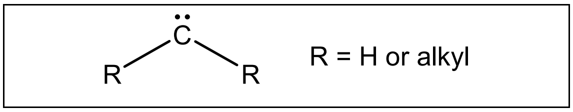
Synthetic Transformation 9.5: Markov. Addition of Br and OR to an Alkene

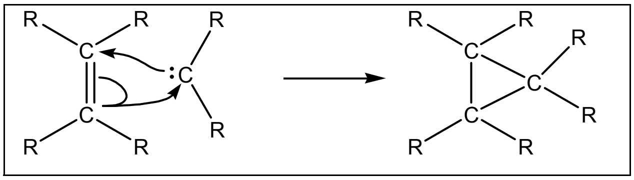


Model 8: Addition of a Carbene to an Alkene

carbene = another exception to Lewis' octet rule

Carbenes are less common than carbocations.



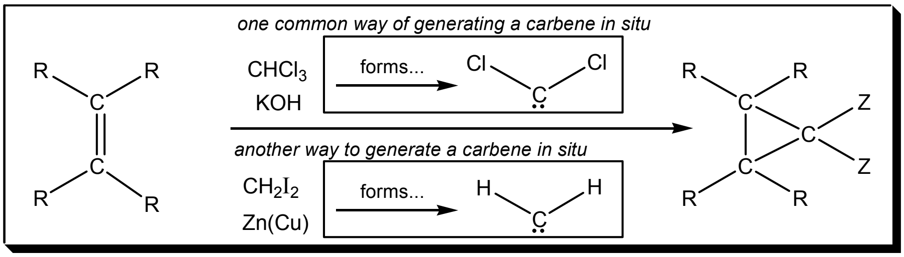


A carbene lacks an octet but has a lone pair, so it will add to an alkene in a similar way as Br^+.

(One key difference: Cyclopropanes do not ring-open easily like epoxides and bromonium ions.)

Carbenes are so reactive they cannot be isolated, so they are generated in situ (in the reaction mixture) and used right away by mixing an alkene with reagents known to give a carbene (e.g., $CHCl_3$ and KOH).

Synthetic Transformation 9.6: Cyclopropane Ring from an Alkene

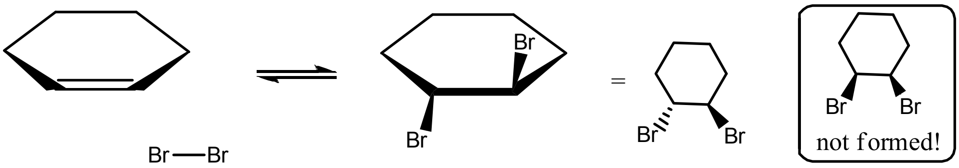

one common way of generating a carbene in situ
CHCl$_3$
KOH
forms...
another way to generate a carbene in situ
CH$_2$I$_2$
Zn(Cu)
forms...

Critical Thinking Questions

14. Construct an explanation for why **cyclopropane** rings are more stable than expoxide rings. Focus on the case of acidic conditions, where cyclopropanes are very stable and epoxides very unstable.

Exercises for Part A

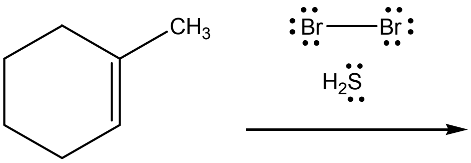
1. Show a mechanism for the following reaction via a bromonium ion intermediate, and explain why the *cis* di-bromide product is NOT formed.



anti addition (*trans* product)

syn addition (*cis* product)

2. Show the mechanism, and draw a likely major product of the following reaction including stereochemistry. Assume H_2S is a stronger nucleophile than bromide ion.



   a. What is the regiochemistry of this reaction: Markovnikov or anti-Markovnikov? Explain your reasoning.

   b. What term describes the stereochemical relationship between Br and SH in the product (the stereochemistry of the product)?

   c. Draw a product that does NOT form in this reaction that has the opposite **regiochemistry** but the correct stereochemistry compared to the product you drew above.

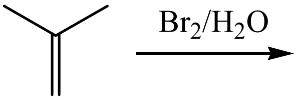
   d. Draw a product that does NOT form that has the opposite **stereochemistry** but the correct regiochemistry compared to the product you drew above.

Exercises for Part B

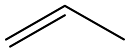
1. Construct an explanation for why the products of CTQ 12 are lower in potential energy than the reactants. (That is, explain why this reaction is downhill.)

2. The 1) and 2) in Synth. Transf. 9.3 designate that the epoxide is first treated with hydroxide, and then, only after waiting for HO^- to react, the acid is added. What would go wrong if we add both reagents, HO^- and HCl, at the same time? (Assume equivalent molar amounts of acid and base.)

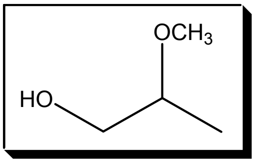
3. Given the reactants below, draw a mechanism for the formation of a product with molecular formula C_4H_9BrO.

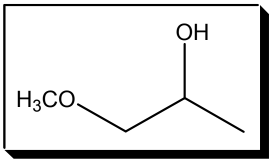


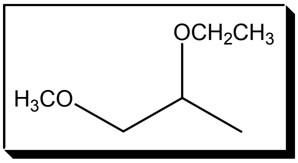
4. Design a synthesis of each of the following targets starting from propene.



propene







5. Read the assigned pages in the text and do the assigned problems.

The Big Picture

Watch out **procrastinators**! Our bag of synthetic tools is starting to get heavy. Your stack of note cards should be growing accordingly. In the next few ChemActivities this stack should grow at an even faster rate. (There are 11 new Synthetic Transformations in ChemActivity 10!!) If you have not started making note cards yet, do not delay. Use the suggestions in the Exercises for Part B of ChemActivity 8. The synthesis problems at the ends of chapters and on quizzes and exams can actually be fun if you know your reactions.

Though mechanisms are still a big emphasis in this part of the course, we are beginning to see some reactions for which the mechanism (if given) is less important than the result. Synth. Transf. 9.2 is an example. Those of you who really love curved arrows will find that knowing the mechanism helps you memorize the reaction. As we go along there will be a few more reactions like this. Some of them have mechanisms that are not well understood or that go far beyond the scope of this course, and you just will have to memorize the reactants, reagents and products without the aid of a mechanism. (When faced with this type of reaction as a student, I sometimes made up a mechanism to help me remember it.)

Common Points of Confusion

- A big distinction in this activity is between **regiochemistry** and **stereochemistry**. To determine regiochemistry ask the question: What region of the molecule will get the nucleophile (the Markovnikov or anti-Markovnikov carbon)? To determine stereochemistry, ask yourself the question: Is the product *cis* or *trans*?
- The other key distinction in this activity is between acidic and basic epoxide ring opening. The argument for why acidic ring opening is Markovnikov centers around the fact that a protonated epoxide is carbocation-like. The argument for basic expoxide ring opening being anti-Markovnikov is based on sterics; in the absence of positive charge, the nucleophile attacks the least-hindered carbon.

ChemActivity 10: Oxidation and Reduction

PART A1: HYDROBORATION/OXIDATION

(What is the regiochemistry and stereochemistry of anti-Markov. addition of H and OH to an alkene?)

Model 1: Lewis Acids (and Lewis Bases)

- **Lewis acid** = molecule with an atom that is electron-deficient (a.k.a. electrophile).
- **Lewis base** = molecule with an atom that is electron-rich (a.k.a. nucleophile).

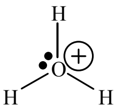
For a given molecule, the **most Lewis acidic** atom = **most electron-deficient atom**.

Table 1a: Selected Elements with (Electronegativities)

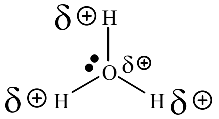
H (2.3)						
Li (0.9)	Be (1.6)	B (2.1)	C (2.5)	N (3.1)	O (3.6)	F (4.2)

Critical Thinking Questions

1. Recall that hydronium ion…



is better represented as...



   a. What is the most Lewis acidic atom on hydronium ion?

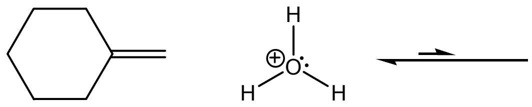
   b. What data in Model 1 allow you to predict that there is more positive charge on H than O?

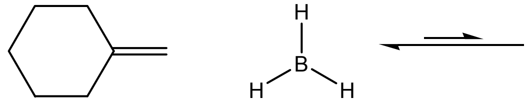
2. Draw a Lewis structure of borane (BH_3).
Note that the boron atom does not have an octet.

   a. Which is more electronegative, **B** or **H** (circle one)?

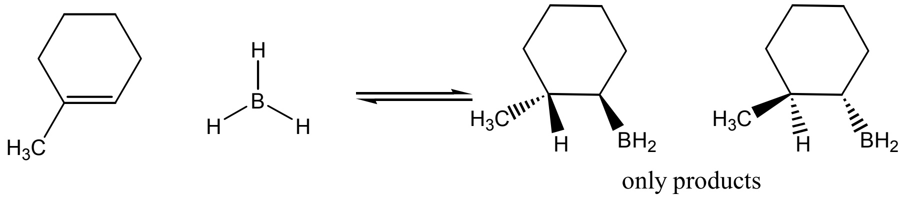
   b. Which atom of **borane** is most Lewis acidic, **B** or **H** (circle one)? Explain your reasoning.

3. Add a curved bouncing arrow to each pair to show the most likely reaction, and draw the resulting carbocation. (In each case, the π electrons make a bond to the **most Lewis-acidic atom**.)

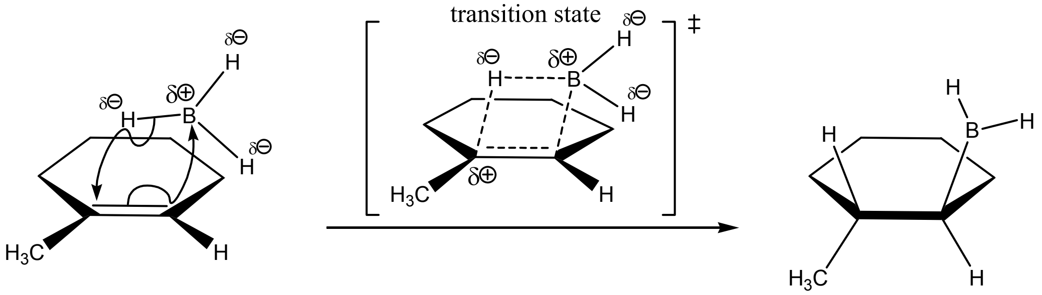




Model 2: Hydroboration (Addition of H and BH_2 to an Alkene)

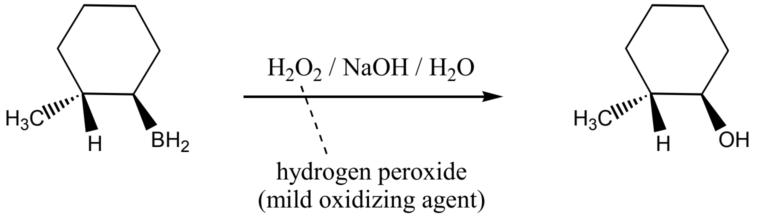


The following mechanism has been proposed to explain these products.

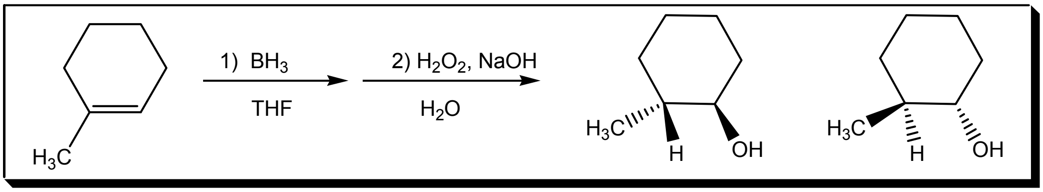


Model 3: Oxidation of BH_2 to OH

BH_2 can be easily oxidized to OH without affecting the stereochemistry or regiochemistry.



Synthetic Transformation 10.1 (same as 8.3): Hydroboration-Oxidation



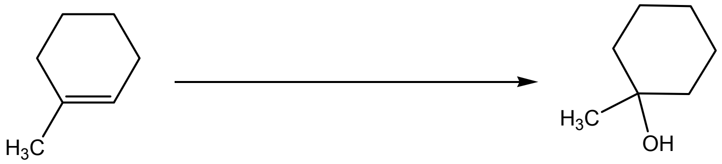
Critical Thinking Questions

4. *Synth. Transf. 10.1* is **stereoselective**. Is the stereochemistry of the addition of H and OH to the π bond **syn** (H and OH added *cis* to each other) or **anti** (H and OH added *trans* to each other)?

5. Explain how the mechanism in Model 2 accounts for the stereochemistry of the products.

6. What is the regiochemistry (**Markov**. or **anti-Markov**.) of *Synth. Transf. 10.1*?

7. Draw reagents (from a previous activity) over the reaction arrow that give the product below.



8. What is the regiochemistry of the reaction in the previous question?

PART A2: CATALYTIC HYDROGENATION

(What is the stereochemistry of **catalytic hydrogenation** of a π bond?)

Model 4: Oxidation and Reduction of Carbon in Organic Chemistry

oxidation = adding O's or taking away H's from *a carbon atom*

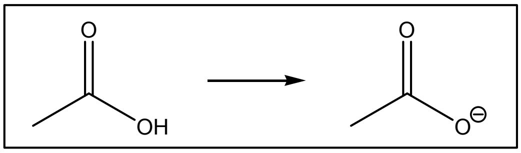
oxidizing agent = any reagent that oxidizes another molecule

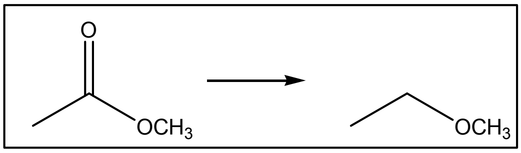
reduction = adding H's or taking away O's from *a carbon atom*

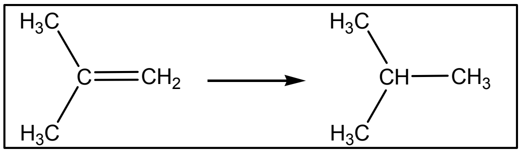
reducing agent = any reagent that reduces another molecule

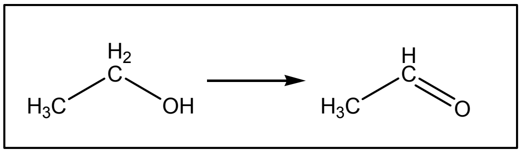
Critical Thinking Question

9. Classify each of the following reactions as oxidation, reduction, or neither.

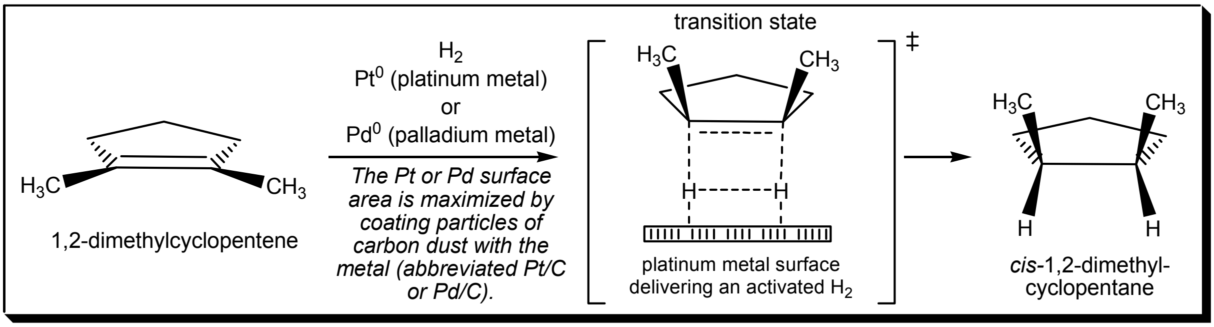








Synthetic Transformation 10.2: Catalytic Hydrogenation



1,2-dimethylcyclopentene

The Pt or Pd surface area is maximized by coating particles of carbon dust with the metal (abbreviated Pt/C or Pd/C).

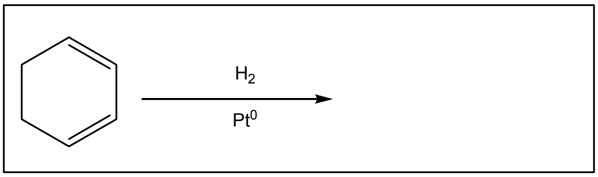
platinum metal surface delivering an activated H_2

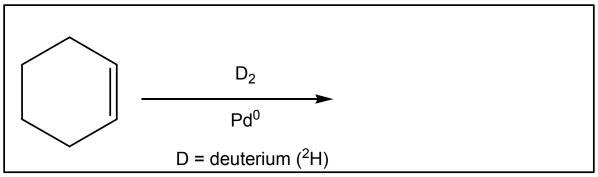
cis-1,2-dimethyl-cyclopentane

Critical Thinking Questions

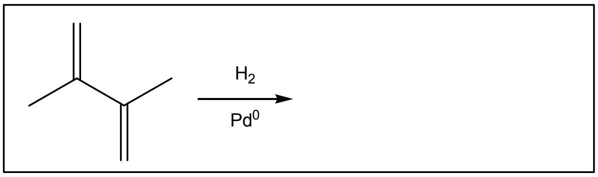
10. What is the stereochemistry (**syn** or **anti**) of the addition of the two H's in *Synth. Transf. 10.2*?

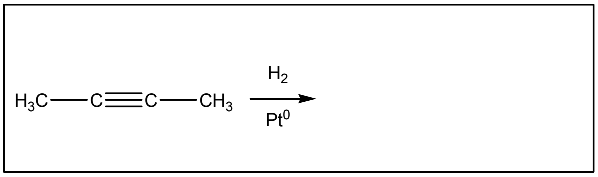
11. Draw the major organic product of each of the following reactions (always assume excess $^{n}H_2$).





D = deuterium (^2H)

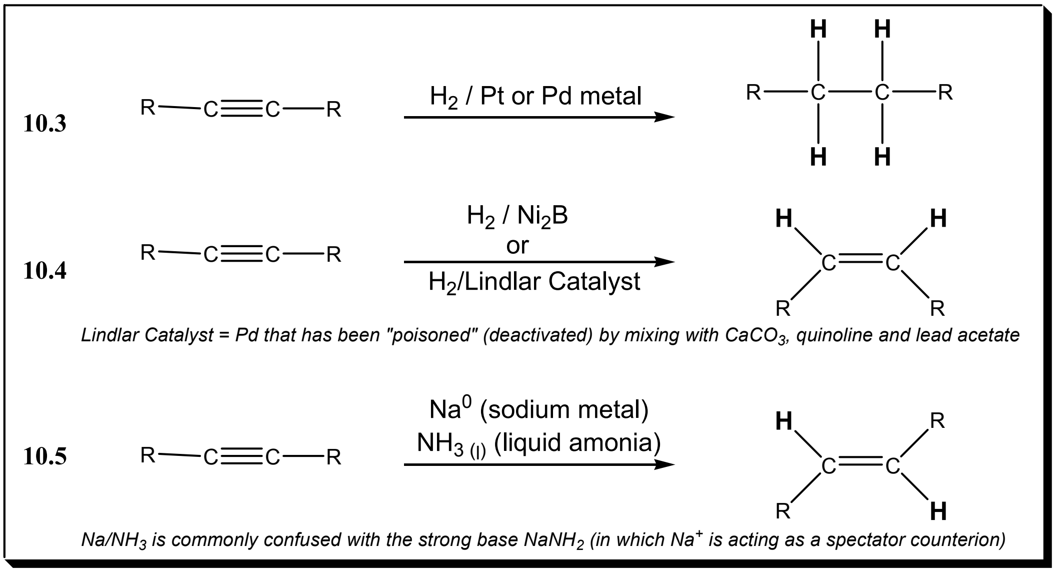




Model 5: Reduction of Alkynes

H_2 and **Pt or Pd metal** will reduce both π bonds of a **triple bond**; however, careful use of a weaker catalyst (e.g. **Lindlar catalyst**) will reduce only one π bond, giving either a *cis* or *trans* alkene.

Synthetic Transformations 10.3-10.5: Stereoselective Alkyne Reductions



Lindlar Catalyst = Pd that has been "poisoned" (deactivated) by mixing with $CaCO_3$, quinoline and lead acetate

Na/NH_3 is commonly confused with the strong base $NaNH_2$ (in which Na^+ is acting as a spectator counterion)

Critical Thinking Questions

12. What evidence in Model 5 tells you it is easier to reduce the first π bond of a triple bond than the second π bond of a triple bond?

13. Summarize the differences among Synth. Transf.s 10.3-10.5 in terms of the products formed.

PART B: OTHER OXIDATION REACTIONS

(Which functional groups can be oxidized?)

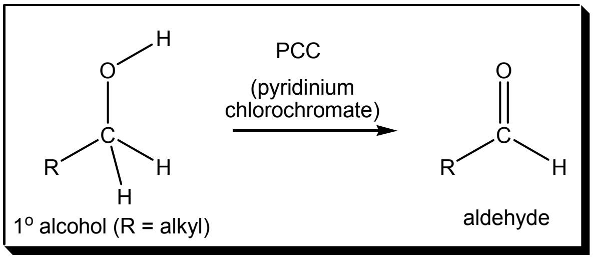
Model 6: Oxidative Cleavage of a C—H Single (σ) Bond

C–H and O–H single bonds (but not C–C single bonds) can be broken easily with oxidizing agents such as **PCC** (*a more selective reagent*) or **$KMnO_4$** (*a stronger oxidizing reagent*).

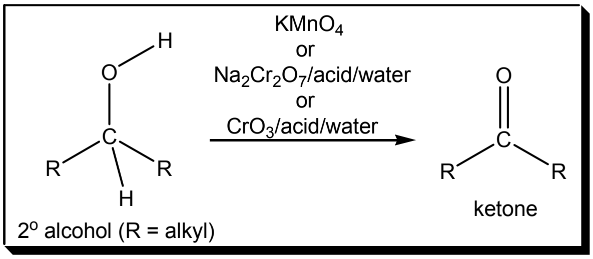
The mechanisms of these reactions are complex, involve multiple radicals, and are beyond the scope of this discussion. (In some instances they are poorly understood.) We will not use curved arrows to make sense of these reactions. Instead, we will focus on C–H bonds broken, and C–O and C=O bonds formed.

Synthetic Transformations 10.6 & 10.7: Oxidation of Primary and Secondary Alcohols

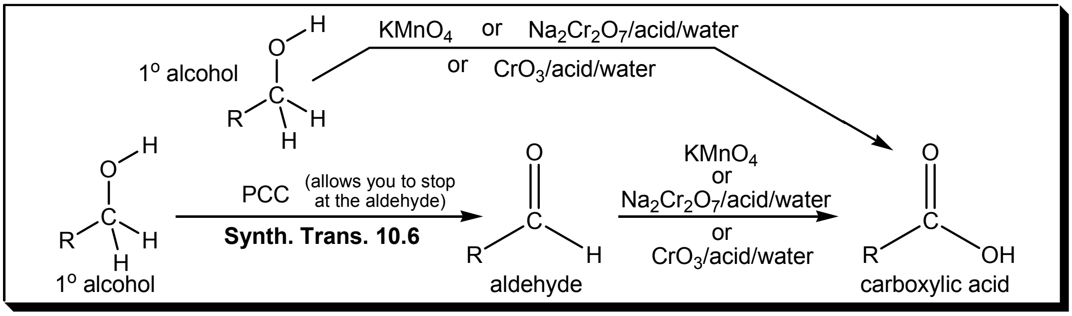
10.6: Oxidation of 1° Alcohol to an Aldehyde



10.7: Oxidation of 2° Alcohol to a Ketone



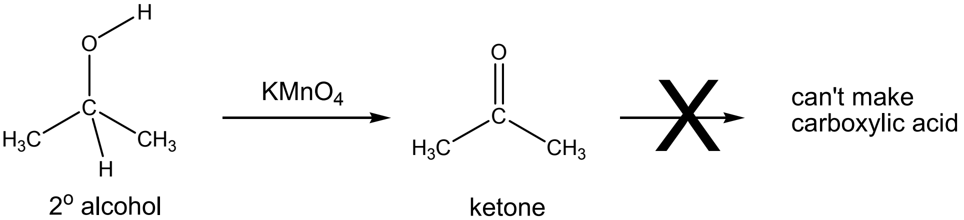
Synthetic Transformation 10.8: Oxidation of a 1° Alcohol or Aldehyde to a Carboxylic Acid



Critical Thinking Questions

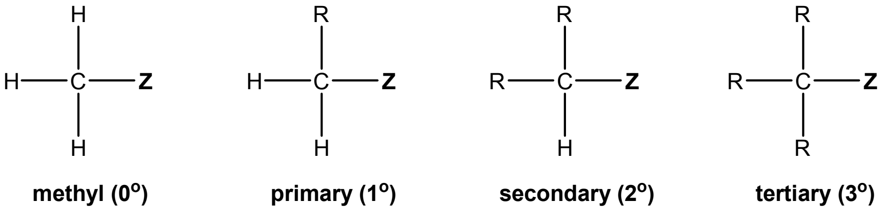
14. Put an **X** through each bond that is broken during each oxidation reaction above.

15. According to Model 6, why can't a 2° **alcohol** (below) be oxidized to a **carboxylic acid**?



Model 7: Primary (1°), Secondary (2°), and Tertiary (3°) Carbons

The words **methyl (0°)**, **primary (1°)**, **secondary (2°)**, and **tertiary (3°)** were used to describe the number of (nonhydrogen) R groups attached to a carbocation carbon (see CA 8). This same naming strategy is used to describe any carbon with one attached “heteroatom,” Z (hetero = other).



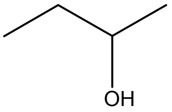
Z = any atom *other than C or H*
(hetroatom)

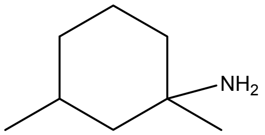
R = alkyl (*not H*)

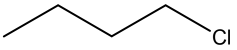
heteroatom = atom other than carbon (or hydrogen), e.g., O, N, F, Cl, Br, etc.

Critical Thinking Questions

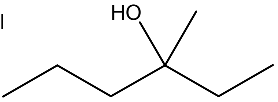
16. For each molecule, identify the heteroatom, and classify the carbon it is attached to as methyl (0°), primary (1°), secondary (2°), or tertiary (3°).

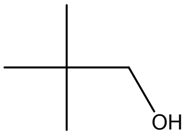






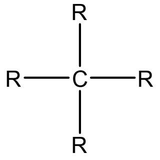
CH_3OH





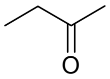
17. Identify the tertiary alcohol in the previous question, and predict if it can be oxidized with any of the oxidizing agents on the previous page. (Check your work: See the underlined statement in Model 6.)

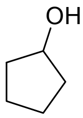
18. The C on the molecule at right is called a **quaternary (4°) carbon.** Explain why there is no such thing as a quaternary alcohol.

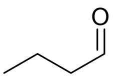


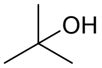
R = alkyl (not H)

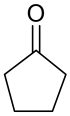
19. Consider the molecules below.
    a. Circle each molecule that can be oxidized using an oxidizing agent on the previous page.
    b. Below each circled species, draw the oxidation product that would result.

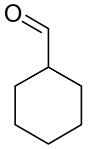






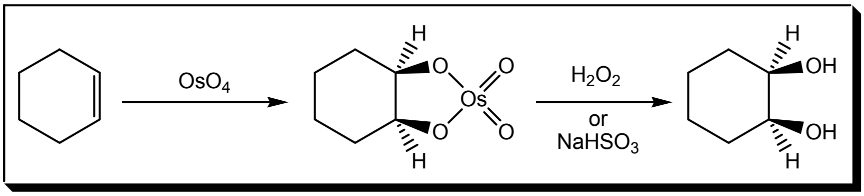






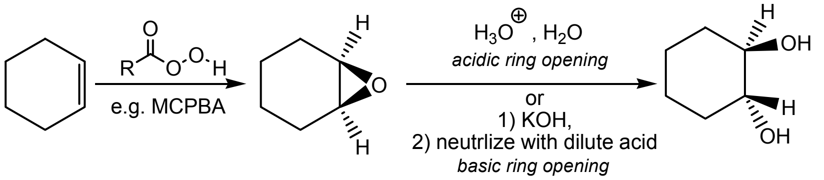
Model 8: Stereoselective Oxidative Cleavage of a π Bond

Synthetic Transformation 10.9: Syn Addition of Two OH Groups to a π Bond



a cold, dilute $KMnO_4$ solution, followed by $KOH_{(aq)}$, can be used in place of the highly toxic OsO_4

Review of Synthetic Transformations 9.3/9.4



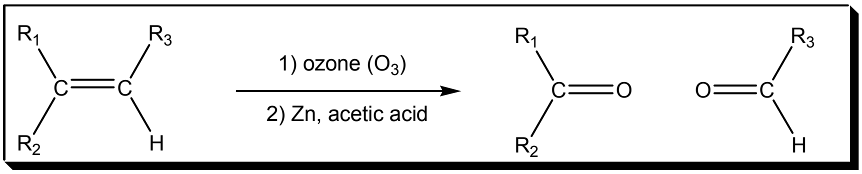
Critical Thinking Question

20. Label one **diol** in Model 8 *trans* and the other *cis.*

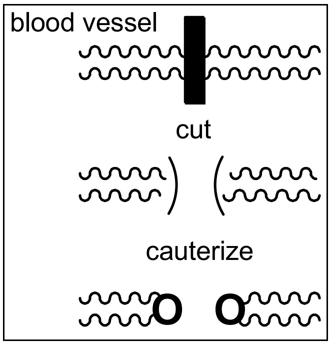
21. Describe how each intermediate product in Model 8 dictates that the two OH groups will be added syn (same side–*cis*) or anti (opposite sides–*trans*) to one another.

Model 9: Oxidative Cleavage of the Entire C=C Bond (both σ and π !!)

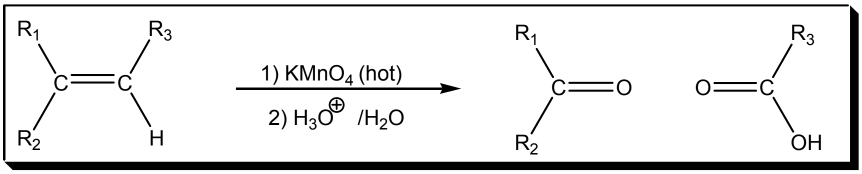
Synthetic Transformation 10.10: Ozonolysis



Think of these reactions as "cut and cauterize" procedures performed on a double bond instead of a blood vessel.



Synthetic Transformation 10.11: Permanganate (MnO_4^-)



Critical Thinking Questions

22. Draw a line (the cut) through each C=C double bond that is broken in Model 9, and state what atom caps (cauterizes) the loose ends resulting from each cut?

23. An H attached directly to a C=C double bond is called a **vinyl hydrogen**. The starting materials in Synthetic Transformations 10.10 and 10.11 each include one vinyl hydrogen.

   a. What happens to a vinyl hydrogen when it is subjected to ozonolysis?

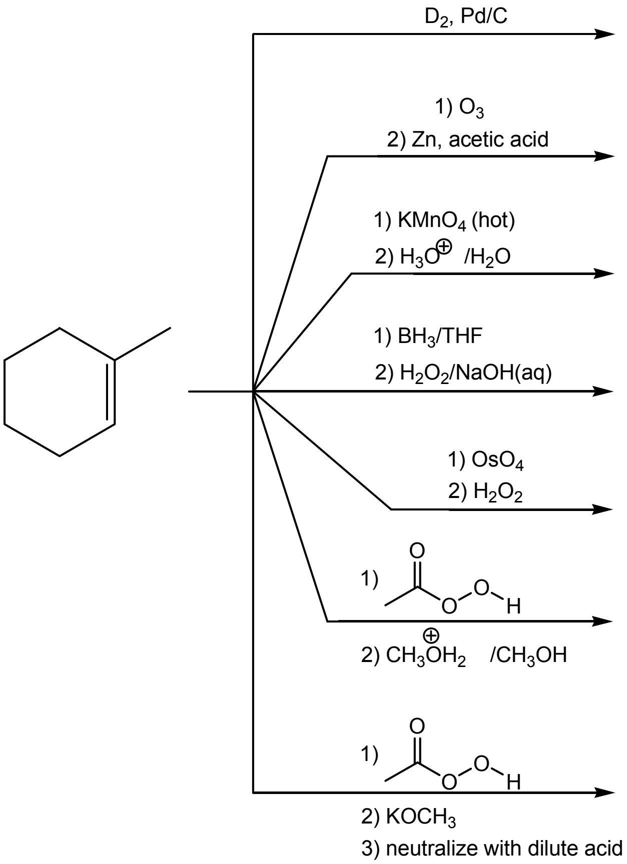
   b. What happens to a vinyl hydrogen when it is subjected to permanganate oxidation?

   c. Label the most oxidized product in Model 9.

   d. Which is a stronger oxidizing agent, **ozone** or **hot $KMnO_4$** (circle one)?

   e. Summarize the key difference between ozonolysis and permanganate oxidation.

24. Draw the major (most likely) product of each reaction.



25. Draw the products of a) ozonolysis and b) permanganate oxidation of propene (CH_3CHCH_2). (Check your work: the molecular formulas of the products of b) are $C_2H_4O_2$ and CH_2O_3)

Exercises for Part A

1. Is the second step of Synth. Transf. 10.1 an oxidation of the organic product or a reduction? Explain your reasoning.

2. Synth. Transf. 10.1 is an updated version of Synth Transf. 8.3. What new information about this transformation was added in this activity? Find your note cards for 8.3, and update them with this new information.

3. Draw a product that does not form in Synth. Transf. 10.1 that has the correct stereochemistry, but the wrong regiochemistry.

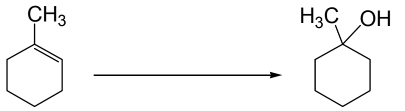
4. Draw a product that does not form in Synth. Transf. 10.1 that has the correct regiochemistry, but the wrong stereochemistry.

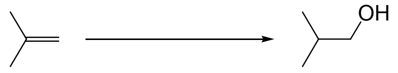
5. Identify each product below as Markov. or Anti-Markov. and syn or anti, as appropriate. Then place one of the following over each reaction arrow.

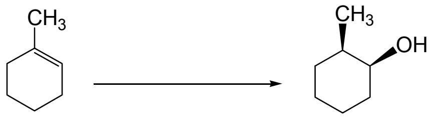
   a. 1) $Hg(OAc)_2$, THF, H_2O 2) $NaBH_4$, NaOH

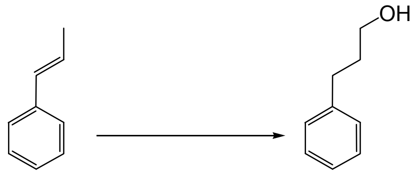
   b. 1) BH_3, THF 2) $H_2O_2/NaOH/H_2O$

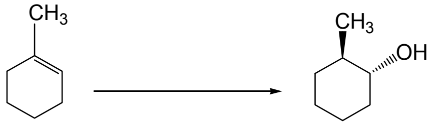
   c. not possible to get this product with reagents a or b

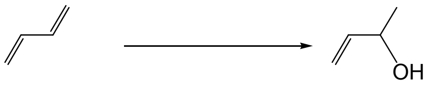




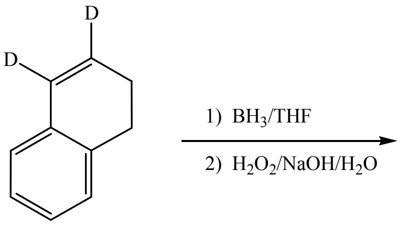


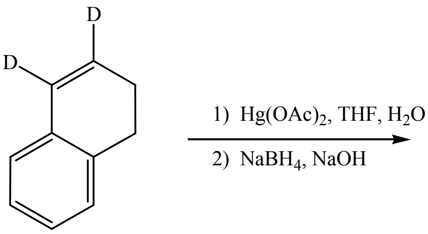




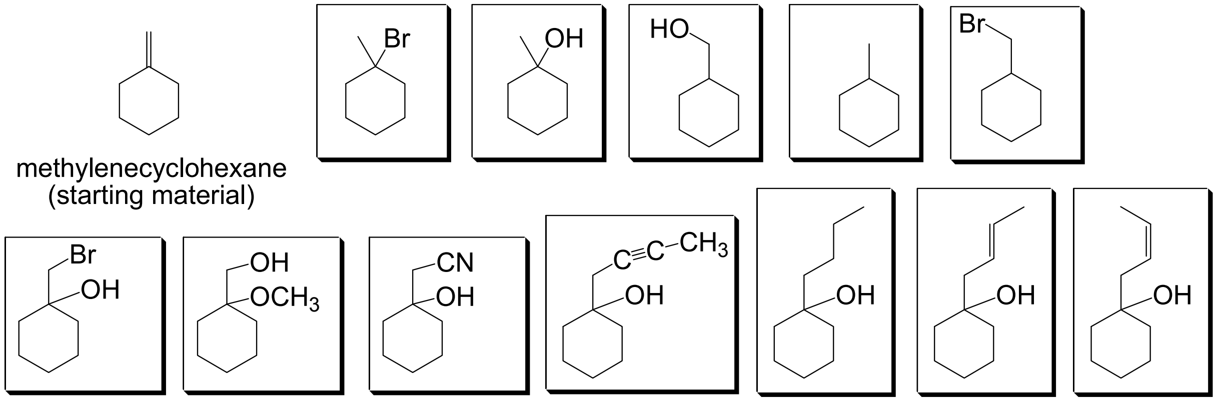


6. Draw the major product of each reaction.

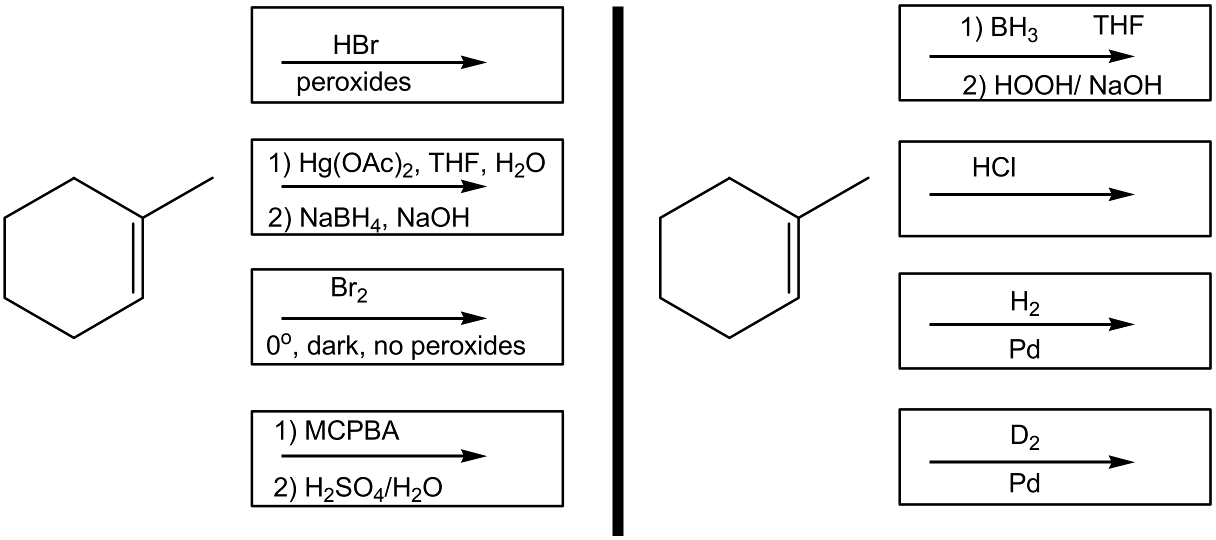




7. Show a synthesis of each of the following target molecules from methylenecyclohexane. (Some syntheses may be only one step.)



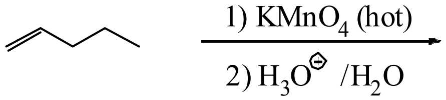
8. Draw the product that results when each set of reagents is mixed with methycyclohexene.



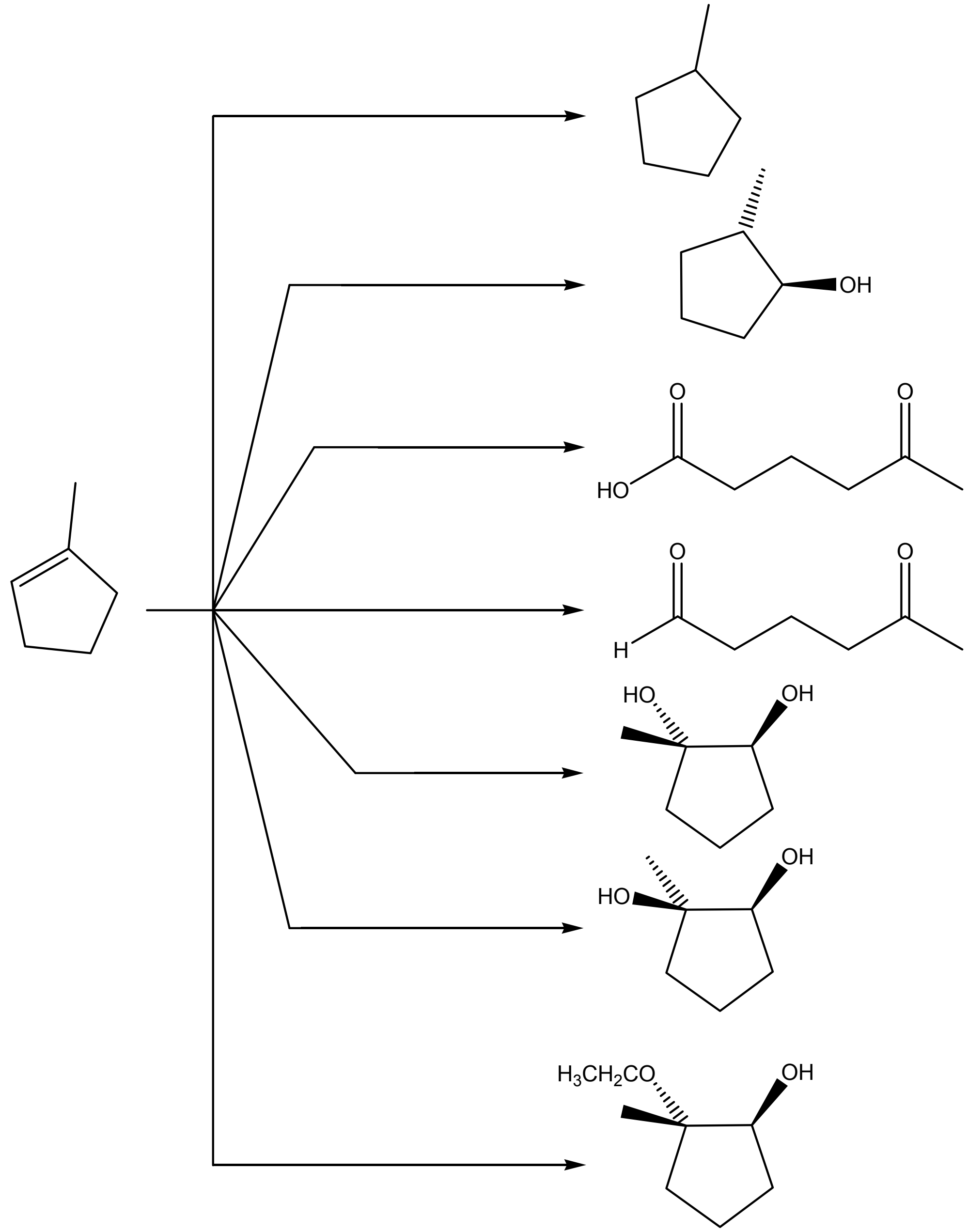
9. Read the assigned pages in your text, and do the assigned problems.

Exercises for Part B

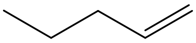
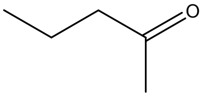
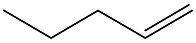
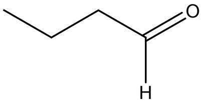
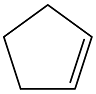
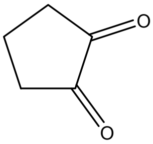
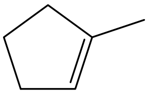
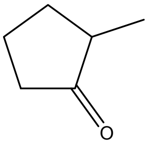
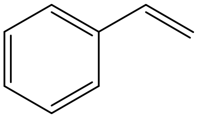
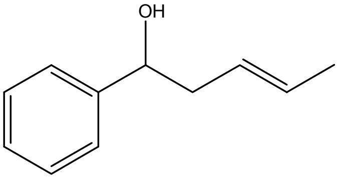
10. Draw the products of the following reaction.



11. Write appropriate reagents over each reaction arrow.



12. Design a synthesis of each of the following targets from the starting material given.

Starting Material	**Target**
	
	
	
	
	

13. Read the assigned pages in your text, and do the assigned problems.

The Big Picture

This ChemActivity is mostly about memorizing new reagents. Few of the reactions in this activity are associated with simple mechanisms. The mechanisms of oxidation and reduction reactions are beyond the scope of this workbook. Whenever possible, as in Synthetic Transformations 10.1, 10.2 and 10.9, an intermediate or partial mechanism is given to help you remember the stereochemistry or some other aspect of the reaction. The bottom line is that you must memorize these reactions. This activity has more new reactions than any other—so you are over the hump, but there is a steady stream of five or six new reactions in each activity to come. Don't get behind!!

If you are having trouble with the synthesis problems this is an indication that you don't know your Synthetic Transformations well enough. The best strategy is a combination of note cards and attempting synthesis problems. Also try switching cards with your study partner or making up synthesis problems for your study partner and vice versa.

Common Points of Confusion

The reagent Na/NH_3 is very commonly confused with the strong base $NaNH_2$. Na/NH_3 is an example of **sodium metal** used as a reagent. Metallic sodium (Na^0) is a potent reducing agent. Na in $NaNH_2$ is Na^+, the +1 counterion for the base H_2N^-.

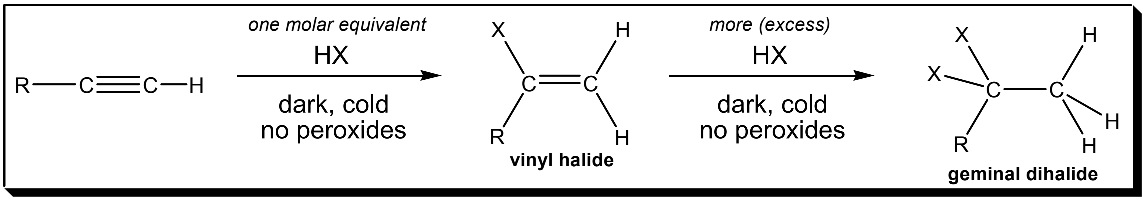
ChemActivity 11: Addition to Alkynes

(What is the mechanism by which an alkyne can be converted to a ketone?)

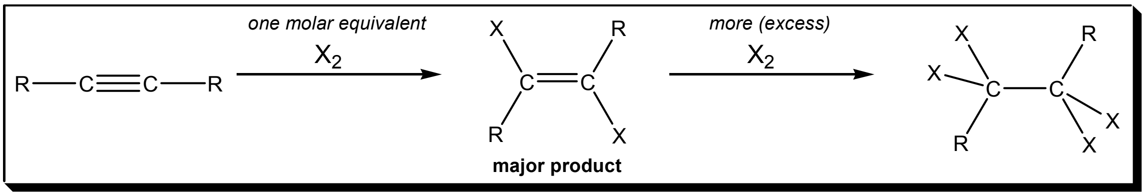
Model 1: Addition of HX and X_2 to Alkynes

Most alkene reactions also work as reactions of one or both of the two π bonds of an alkyne.

Synthetic Transformation 11.1: _______________ Addition of H and X (X = Cl, Br, or I)



Synthetic Transformation 11.2: Addition of X_2 (X = Cl or Br)



Critical Thinking Questions

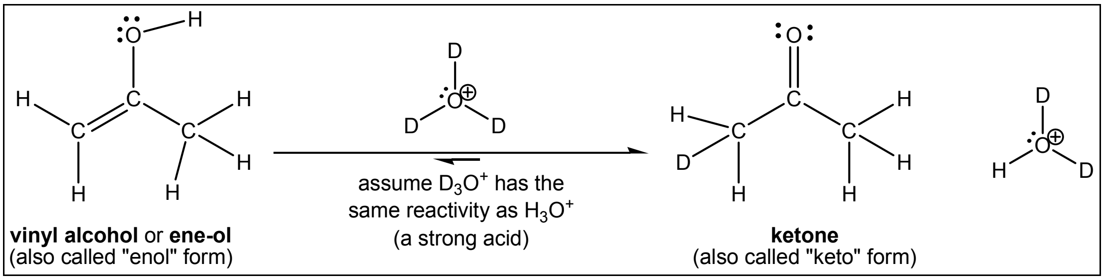
1. Fill in the blank in the title of Synthetic Transformation 11.1 with the words "**Markovnikov**" or "**anti-Markovnikov**," as appropriate.

2. Label the **vinyl halides** in Model 1 ***cis, trans*****,** or **neither**, as appropriate. (A **vinyl group** is any group directly attached to a C=C double bond, so a vinyl bromide has a Br attached to a C=C.)

3. What evidence is there in Model 1 that Synth. Transf. 11.2 proceeds via a cyclic intermediate such as a bromonium ion?

4. ***Gemini*** is the astrological symbol known as "the twins." Construct an explanation for why the final products of the synthetic transformations above are called **geminal dihalides.**

Model 2: Enol to Keto Tautomerization of Vinyl Alcohols


vinyl alcohol or ene-ol
(also called "enol" form)
assume D_3O^+ has the same reactivity as H_3O^+
(a strong acid)
ketone
(also called "keto" form)

D_3O^+ is used as an acid in the reaction above to help you track the course of the reaction. However, the same reaction takes place with any acid. This reaction is called an **enol-to-keto tautomerization**.

In fact, the keto form is normally favored so heavily over the enol form that **most enols are unstable in solution**. (A polar solvent can facilitate a **tautomerization** to the keto form, even without a catalyst.)

Critical Thinking Questions

5. Construct a mechanism for the reaction shown in Model 2.

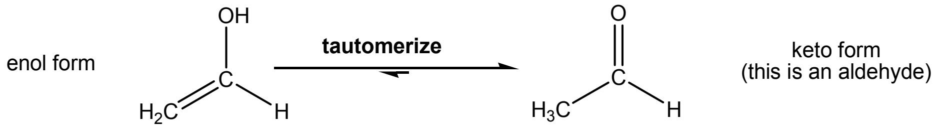
6. Which form is lower in potential energy: **keto** or **enol** (circle one)?

7. Speculate about the etymology (origin) of the name "enol."

Memorization Task 11.1: Tautomerizations

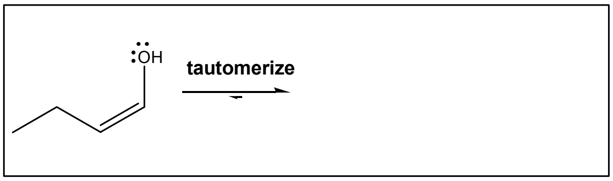
Know how to recognize or draw the keto and enol forms of a molecule, and know the mechanism of a keto-enol tautomerization under acid- and base-catalyzed conditions.

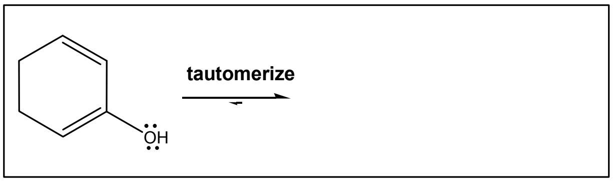
However, unless you are specifically asked to do so, you do not need to show the mechanism of a tautomerization. Simply write the word "tautomerize" over the reaction arrow…

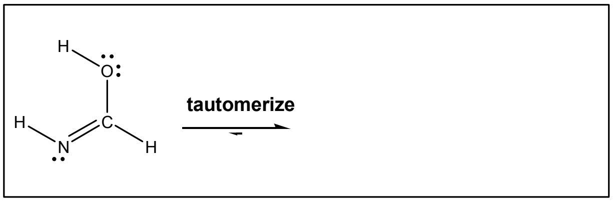


8. Draw the missing keto or enol form of each of the following.

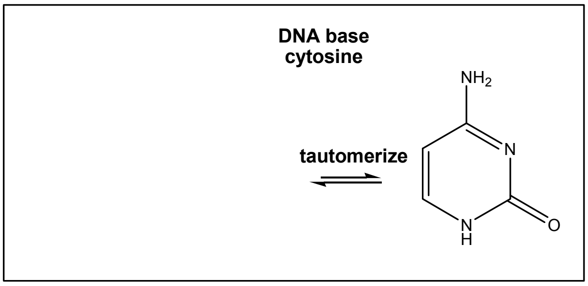
enol form keto form

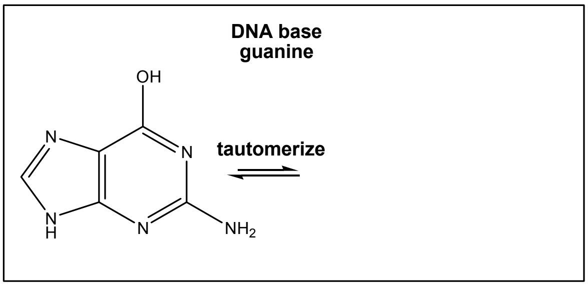




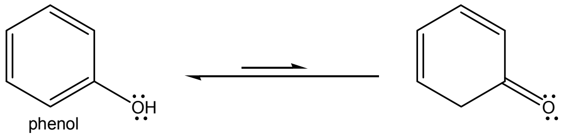


enol form keto form

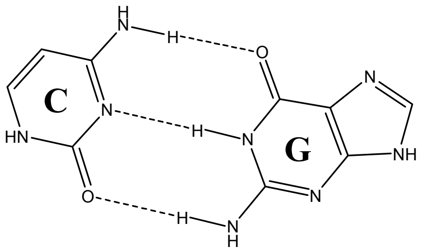


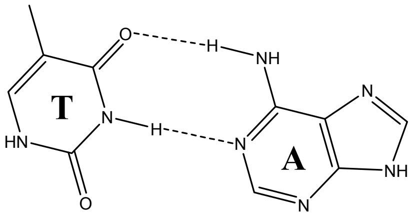


9. Construct an explanation for why **phenol** and similar enols are favored over their keto forms. That is, their enol-to-keto tautomerizations are uphill instead of downhill.



Historical Note on the Discovery of the Structure of DNA by Watson and Crick





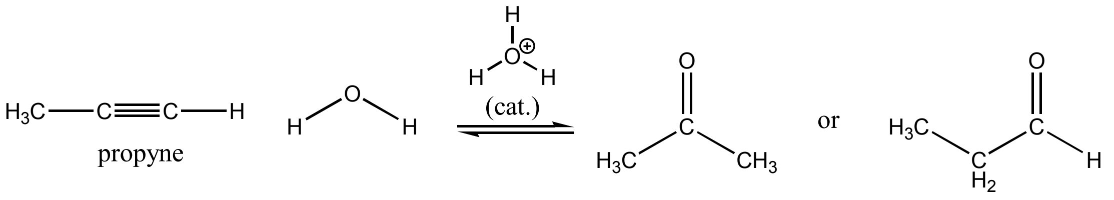
Hydrogen bonds between the DNA base pairs (CG and TA) form the attachments between two strands of a DNA double helix. Unexpectedly, the keto forms of the bases (shown above) are employed in DNA despite the fact that the enols are benzene-like. (The enol forms are favored when the bases are not incorporated into DNA.) This stumped Linus Pauling, who many consider the greatest chemist of the 20th century. Pauling was beaten to the discovery of these base pairings by 25-year-old American zoologist James D. Watson, who won the Nobel Prize for this discovery. I met Watson once, and he sheepishly admitted that as a student he "avoided his chemistry classes as much as possible."

Pauling, who was steeped in the teachings of traditional organic chemistry, assumed incorrectly that each of the DNA bases preferred their benzene-like enol form. Watson was just naïve enough about organic chemistry to make models of the keto forms. (Perhaps he memorized that keto is favored over enol, but forgot the exception to this rule for benzene-like molecules?)

The moral of this story is NOT that it pays to skip organic chemistry class, but rather that science is constantly changing and YOU may someday participate in this process. Eventually, everything in this book is going to be changed, improved, or discarded based on future research conducted by someone like you.

Model 3: Acid-Catalyzed Addition of H and OH to an Alkyne

Only one of the products shown below is observed in this reaction.



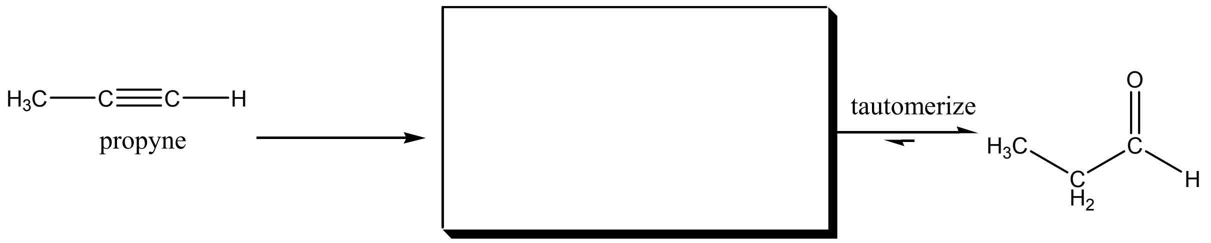
Critical Thinking Questions

10. Draw the mechanism and circle the more likely product of the addition reaction in Model 3. (Do not show the mechanism of the tautomerization–just write "tautomerize.")

    a. Explain why the circled product forms preferentially.

    b. Is the reaction above **Markovnikov** or **anti-Markovnikov** (circle one)?

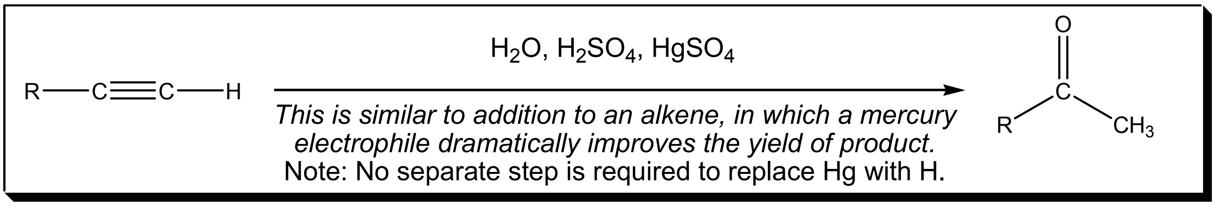
11. In the box *below*, draw the enol that would give rise to the product shown.



    a. Is this reaction **Markovnikov** or **anti-Markovnikov** (circle one)?

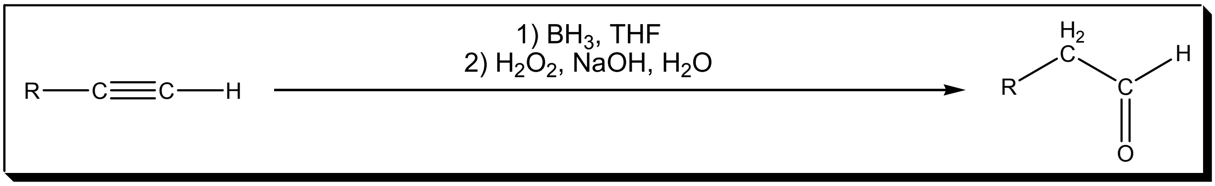
    b. Over the reaction arrow, write reagents that would accomplish this transformation.

Synthetic Transformation 11.3: Markov. Addition of H_2O to an Alkyne

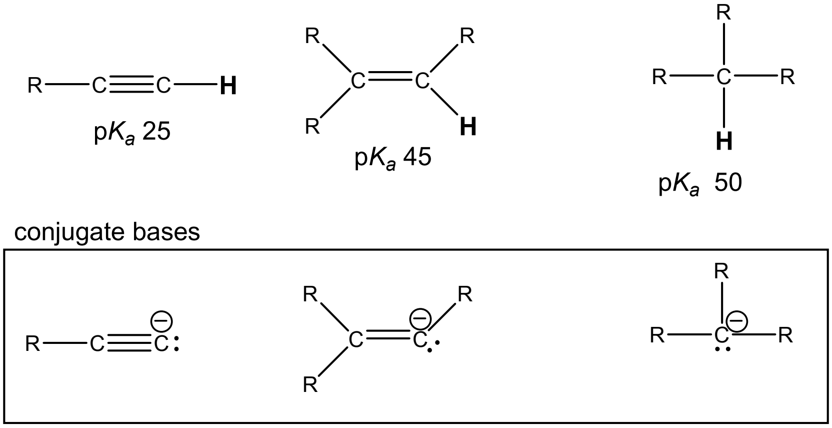


This is similar to addition to an alkene, in which a mercury electrophile dramatically improves the yield of product.
Note: No separate step is required to replace Hg with H.

Synthetic Transformation 11.4: anti-Markov. Addition of H_2O to an Alkyne



Model 4: Alkyne Acidity (compared to alkenes and alkanes)



Critical Thinking Questions

12. Based on the pK_a data, circle the molecule in Model 4 that is most acidic.

    a. Label each conjugate base with the type of orbital the lone pair resides in. (*Hint*: What is the hybridization state of the atom holding the lone pair?)

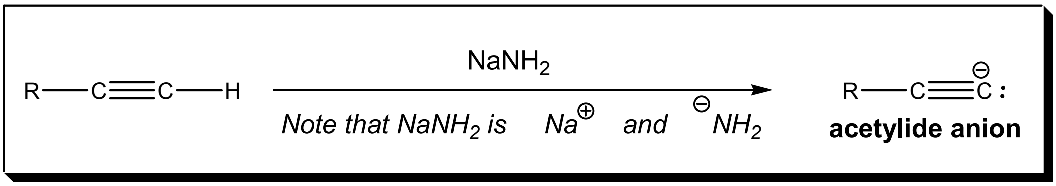
    b. Label each orbital holding a lone pair with its "percent *s* character" (percent red clay).

    c. Which is lower in potential energy, an ***s* orbital** or ***p* orbital** (circle one)?

    d. Construct an explanation for the pattern in the pK_a data above.

13. Which, if any, of the conjugate acids in Model 4 will react significantly with $NaNH_2$? Explain your reasoning.

Synthetic Transformation 11.5: Deprotonation of an Alkyne



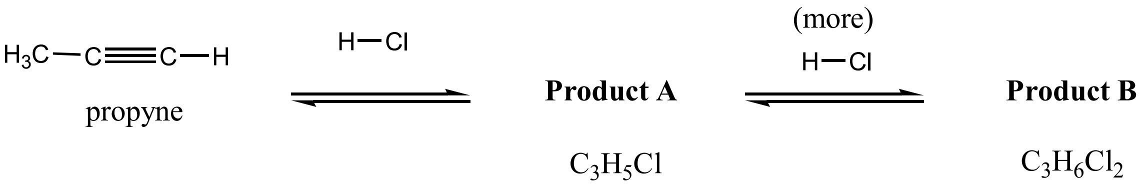
14. An **acetylide anion** is a potent and useful **electrophile** or **nucleophile** (circle one, and explain your reasoning).

Exercises

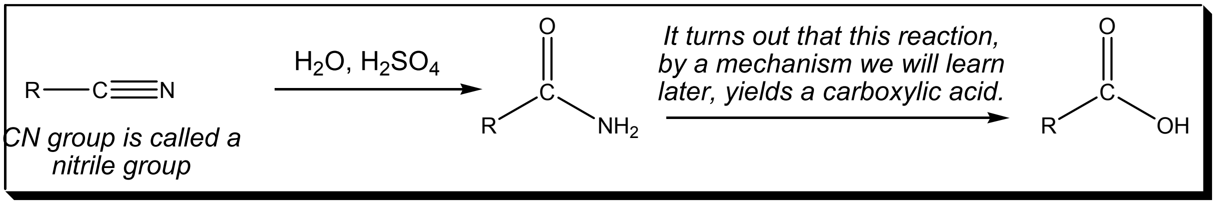
1. When propyne is treated with H–Cl, two different products are observed (A and B).

- Product A is an intermediate product on the way to Product B.
- The molecular formula of each product is given below.
- Product B is observed only when excess HCl is added.

Draw a mechanism that accounts for the formation of these two products, A and B.

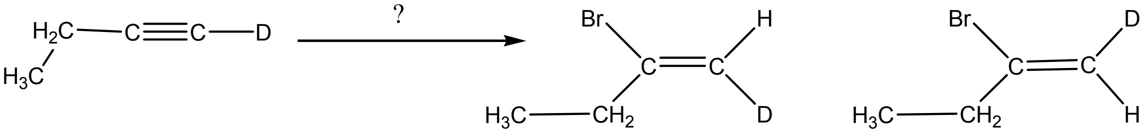


Synthetic Transformation 11.6: Nitrile Hydrolysis

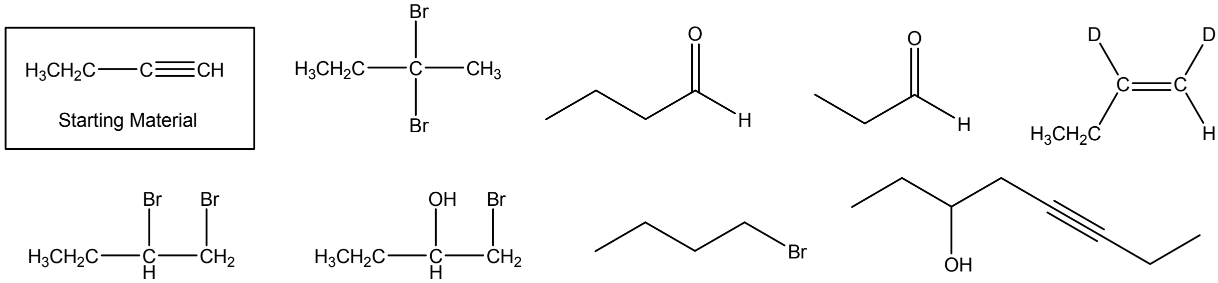

R—C≡N
CN group is called a nitrile group
H2O, H2SO4
It turns out that this reaction, by a mechanism we will learn later, yields a carboxylic acid.
O
C
R
NH2
O
C
R
OH

2. Use curved arrows to show the mechanism of the first part of **Synthetic Transformation 11.6: nitrile hydrolysis**.

3. Over the reaction arrow, write the reagent(s) that produce the products shown.
In each case, label the products shown Markov. or anti-Markov.. and *E* or *Z*.



4. Design a synthesis of each of the following targets using 1-butyne as the only source of carbon.



5. Read the assigned pages in the text, and do the assigned problems.

The Big Picture

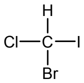
Keep working on those synthesis problems. They won't go away. Luckily there is very little new in this activity because the pi bonds of an alkyne behave very similarly to the pi bonds of an alkene. Alkynes are slightly more interesting than alkenes when you add water across the first pi bond since the result is an enol that will spontaneously tautomerize to the lower PE keto form (but watch for benzene rings!).

The fact that a strong base can be used to pull an H off an *sp*-hybridized carbon is another wrinkle that will be explored in upcoming activities. As a preview, note that the resulting acetylide anion is a carbon nucleophile that can be combined with carbon electrophiles to make a wide range of carbon-carbon bonds. The only example of this we have discussed so far is nucleophilic epoxide ring opening.

Common Points of Confusion

(Repeat of the issue from CA 10) The reagent Na/NH_3 is very commonly confused with the strong base $NaNH_2$. Na/NH_3 is a rare example of sodium used as a reagent. Metallic sodium (Na^0) is a potent reducing agent. Na in $NaNH_2$ is Na^+, the +1 counterion for the base H_2N^- used to remove an H from an *sp*-hybridized carbon, as in Synthetic Transformation 11.5.

ChemActivity 12: Chirality

BUILD MODELS: 

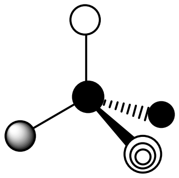
and 2-chlorobutane

PART A: CHIRALITY

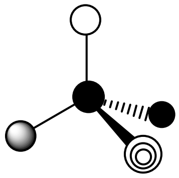
(How can you tell if an object is chiral?)

Model 1: Same or Not the Same

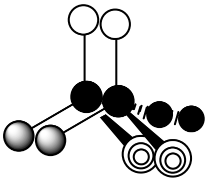
Recall that two molecules are the **same** if models of them can be **superimposed** without breaking bonds.



and



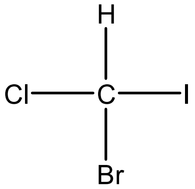
identical if



super-imposable

Critical Thinking Questions

1. (E) Make two identical models of the following molecule, and **confirm that they can be superimposed on one another as shown above**. Use any four different colors to represent the four attached atoms. If your set has green, orange and purple, use the following color code.



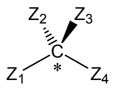
green ball = chlorine atom
orange ball = bromine atom
purple ball = iodine atom

2. Switch any two balls on one of your models (leave the other model unchanged). Is this new model identical to your original model?

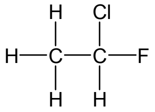
3. Which of the following words describe(s) the relationship between these two models? (Circle more than one choice, if appropriate.)
   a. **same** (or **conformers** = can be made identical via single-bond rotation)
   b. **configurational stereoisomers** (same atom connectivity, but not identical)
   c. **constitutional isomers** (same formula, different atom connectivity)
   d. **mirror images** (look like reflections of one another in the mirror)

Model 2: Chiral Centers (Stereogenic Atoms)

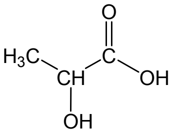
It turns out there are two ways to arrange four different groups around a tetrahedral atom (usually C), and that these two arrangements will be mirror images of one another. Such a carbon is often marked with an *, and called a **stereogenic carbon** because its presence generates two configurational stereoisomers. Stereogenic atoms are also called **chiral centers** (*cheir* is Greek for “handed”).



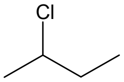
stereogenic carbon (chiral center) has 4 different groups



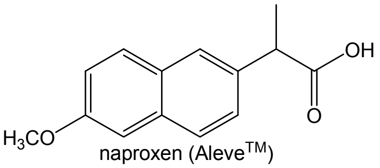
1-chloro-1-fluroroethane



lactic acid



2-chlorobutane



naproxen (Aleve^{TM})

Critical Thinking Questions

4. There is one **chiral center** in each molecule in Model 2. Mark this chiral center with an *.

5. Figure 12.1 shows both possible configurational stereoisomers of 2-chlorobutane.

   a. Make a model of 2-chlorobutane so that it looks like the stereoisomer **on the left side of Figure 12.1** (Check your model by holding it up to the drawing.).

   b. Can you make your model look like the drawing on the right side of Figure 12.1 without breaking any bonds?

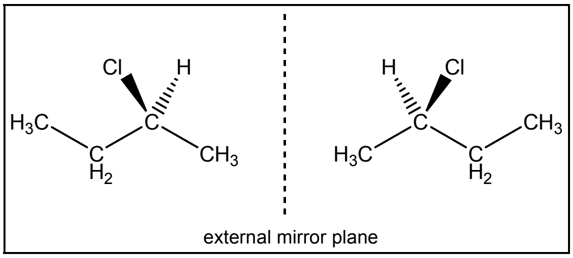


Figure 12.1: Stereoisomers of 2-chlorobutane

Memorization Task 12.1: Trick for drawing the mirror image of a chiral molecule

You can transform your model of the stereoisomer on the left into its mirror image (the stereoisomer on the right) by **switching any two groups attached to the chiral center** (as you did in CTQ 2).
This trick can be used to generate a mirror image of any molecule with one chiral center.
One way to show this on paper is to change a wedge bond into a dash bond or vice versa.

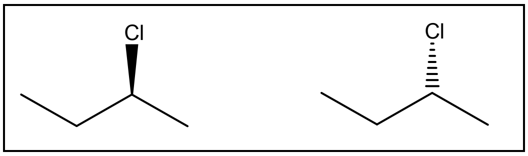


Figure 12.2: Skeletal representation of 2-chlorobutane stereoisomers

   c. How can you tell that the H on the chiral carbon on the left in Fig. 12.2 is going into the paper?

   d. Switch two groups on your model of 2-chlorobutane, and confirm that it looks like the drawing of 2-chlorobutane on the right side of Figure 12.1 **and the right side of Fig. 12.2**.

Term Introduction

Term	Definition	Term describes…	Origin
chiral	= not identical to its mirror image	a property *(like "round" or "green")*	*cheir* is Greek for "handed"
enantiomer	= the mirror image of a chiral object or molecule	a relationship *(like "son" or "sister")*	*enantio* is Greek for "opposite"
racemic mixture	= a 1:1 mixture of a pair of enantiomers	a special sample *(like the passengers on Noah's Ark)*	From *racemic acid* found in wine (*acin* is Latin for grape)

Critical Thinking Questions

6. Draw a molecule that is…
   a. **not chiral** (achiral)

   b. **chiral**

   c. Draw the **enantiomer** of the chiral molecule you drew in part b.

7. Give an example of an everyday object that is…
   a. **not chiral** (achiral)

   b. **chiral**

   c. Describe the **enantiomer** of the chiral object you named in part b.

8. Explain why there is a **racemic mixture** (or very close to one) of shoes in this classroom.

Model 3: Optical Activity: The Discovery of Chiral Molecules

In the early 1800's, French physicist Jean-Baptiste Biot discovered that shining a beam of polarized light through a solution of certain pure substances caused a rotation in the polarization plane of the light.

Such molecules were deemed **optically active.**

Polarimetry studies show that nearly all biological molecules are optically active. In fact, some molecules have one biological function while their enantiomers have a totally different function.

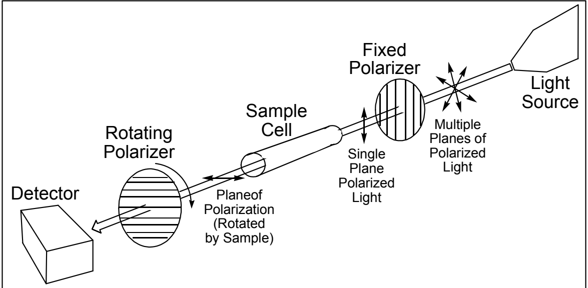

Fixed Polarizer
Light Source
Multiple Planes of Polarized Light
Single Plane Polarized Light
Sample Cell
Rotating Polarizer
Detector
Planeof Polarization (Rotated by Sample)

Figure 12.3: Schematic of a Polarimeter

Memorization Task 12.2: Explanation for Polarimeter Results

It took nearly the whole 19th century for scientists to reach the following conclusions: A solution of…

- a given **chiral** molecule will rotate the plane of polarized light some unpredictable angle (α)
- its **enantiomer** will rotate the plane of polarization an equal angle in the **opposite direction** ($-\alpha$)
- an **achiral** molecule will NOT rotate the plane of polarization.
- a **racemic** mixture will NOT rotate the plane of polarization.

There is no reliable way to look at a structure and predict the size or direction of the rotation of the plane of polarization unless you have already measured alpha (α) for its enantiomer.

Memorization Task 12.3: The Old System for Naming Chiral Molecules: (+) and (–)

Based on these early studies, enantiomers were first named based on whether the plane of polarization was rotated clockwise (+) or counterclockwise (–).

There is now a new system (which we will learn in the next section) in which molecules are categorized as either **right-handed** or **left-handed** based on their structure. There is no correlation between the right/left system (called **R/S** for the Latin words for ***rectus*** and ***sinister***) and the old (+)/(–) system.

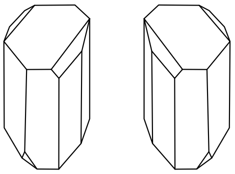
Memorization Task 12.4: Physical Properties of Chiral Molecules

In a laboratory without a polarimeter, it is very difficult to tell enantiomers apart because they have the same physical properties such as melting point, boiling point, solubility, density, etc.; yet your nose can distinguish some enantiomers. For example, (+) and (–)-**carvone** are the flavors caraway and spearmint. (+)-Carvone fits a specific receptor in your nose the way only a right hand fits properly in a right glove. Many drugs, including ibuprofen, have biological activity while their enantiomer is inert or even toxic.

Critical Thinking Questions

9. (+)-**tartaric acid** rotates **plane-polarized light** 12° clockwise ($\alpha_D = +12$). What is α_D for (–)-tartaric acid?

10. In 1848 French chemist Louis **Pasteur** noticed that a solution of a chemical derived from wine grapes, tartrate (the conjugate base of tartaric acid, which is also called racemic acid), did NOT rotate polarized light. By looking through a microscope Pasteur found that crystals made from this solution had two different shapes—and that the shapes were mirror images of each other. He painstakingly separated the two crystal types (shown at right) into piles and made a solution from each pile. The resulting two solutions exhibited optical activity of equal size, but opposite sign.



Tartrate Crystals

   a. Construct an explanation for why Pasteur's tartrate solution was NOT optically active.

   b. What is the origin of the term **racemic mixture**?

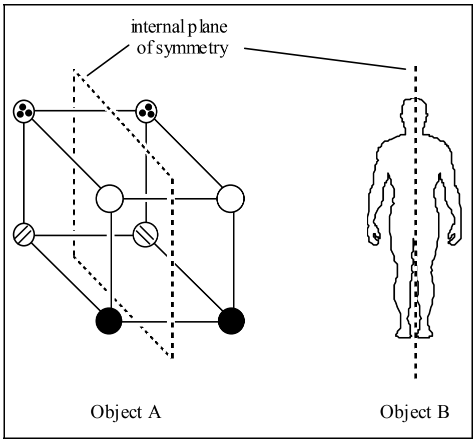
   c. What term describes the relationship between the molecules that Pasteur painstakingly separated on the basis of crystal shape using tweezers and a microscope?

Model 4: Internal Plane of Symmetry (Internal Mirror Plane)

It is always true that an object or molecule with an **internal mirror plane** is not chiral.

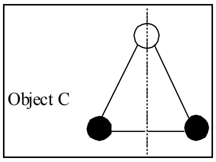
Not chiral = **achiral** = identical to its mirror image.

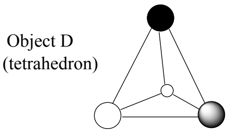
An object or molecule with no internal mirror plane is **chiral** (different from its mirror image).



Critical Thinking Questions

11. Object C has an obvious mirror plane, marked with a dotted line, and a not-so-obvious one. (Assume the circles are spheres of equal size.)
    a. Where is the second mirror plane on Object C?
    b. Where is the mirror plane on Object D?

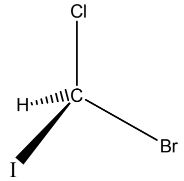




    c. Draw a modification on one of Object D's spheres so as to make it chiral.

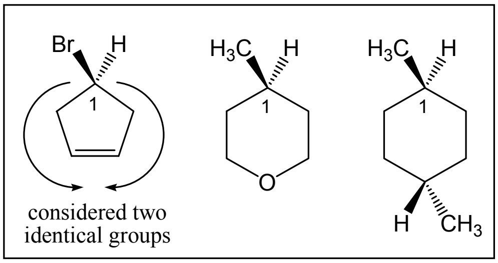
12. Draw a tetrahedron on the molecule below by drawing lines connecting the H, Cl, Br, and I.

13. Based on the definition of chiral in Model 4, explain why an sp^3 carbon with four different groups attached must be chiral.

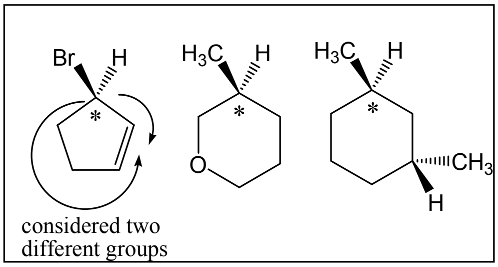


Model 5: Chiral Centers on Rings

Not Chiral



Chiral



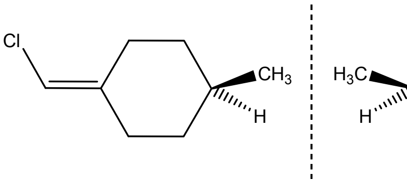
Critical Thinking Questions

14. Confirm that each molecule in the "Not Chiral" box has an **internal mirror plane** and that each molecule in the "Chiral" box does not.

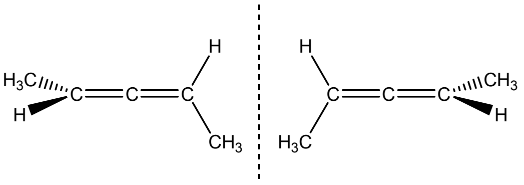
15. Construct an explanation for why each carbon indicated with a "1" is considered to have **two identical groups**, while each carbon with an * is a chiral center with **four different groups**.

Model 6: Chiral Molecules with No Chiral Centers

Very rarely, we will encounter a **chiral molecule with no chiral centers**.



external mirror plane



external mirror plane

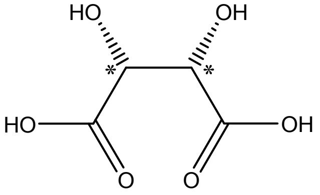
Critical Thinking Questions

16. Confirm that there are no chiral centers in either molecule in Model 6.

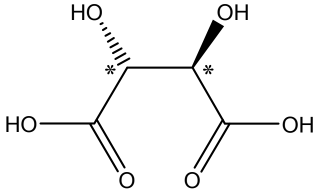
17. Do any of the molecules in Model 6 have an internal mirror plane? If so, describe where it is.

18. What conclusion can you draw from the fact that none of the molecules in Model 6 have an internal mirror plane?

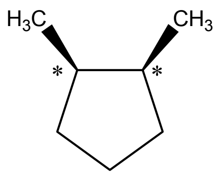
Model 7: Molecules with Two Chiral Centers

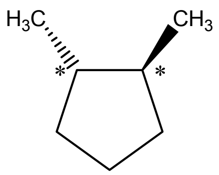


meso-tartaric acid



(+)-tartaric acid





Critical Thinking Questions

19. Confirm that each * in Model 7 marks a chiral center with four different groups attached.

20. Two of the molecules in Model 7 are **not chiral even though they have chiral centers**! Identify the two achiral molecules by marking each one's internal mirror plane.

Term Introduction

meso compound	= molecule with chiral centers that is **not chiral**	*a meso compound always has two or more chiral centers and an* **internal mirror plane**

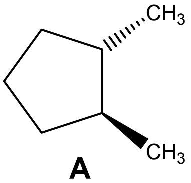
21. Label each *meso* compound in Model 7.

BUILD MODELS: TWO PER GROUP of trans 1,2-dimethylcyclopentane

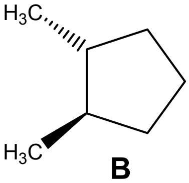
PART B: ABSOLUTE CONFIGURATION

(How do you name the two different kinds of *trans*-1,2-dimethylcyclopentane?)

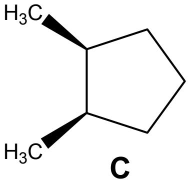
Model 8: Sample of Molecules with Molecular Formula C_7H_{14}



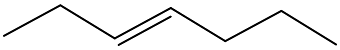
A



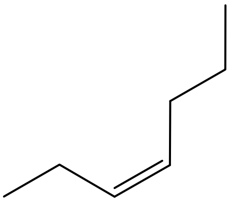
B



C



D



E

Critical Thinking Questions

22. Label A-E in Model 8 with the terms *cis*, *trans,* and/or *meso,* as appropriate. Two terms may apply. (Review) *meso* = molecule with chiral centers and an internal mirror plane such that it is not chiral.

23. **Make separate models of A and B.** Check to make sure the wedge and dash bonds on the paper match the methyl groups on your models by holding each completed model up to the paper.

24. Are A and B the same? **Confirm your answer by testing if your models are superimposable.** (That is, can they be placed on top of one another so that all their atoms match up?)

Term Introduction

diastereomers	= a pair of molecules that are configurational stereoisomers **but not enantiomers**	a relationship *(like "son" or "sister")*

25. What term best describes the relationship between each of the following? Choose from:

same/conformers **enantiomers** **diastereomers** **constitutional isomers** **different formula**

a. B & C c. D & E e. A & E

b. A & C d. A & D f. A & B

a. B & C b. D & E c. A & E

d. A & C e. A & D f. A & B

26. (Check your work) If you decided that A and B in Model 8 are the same/conformers, go back and build models of A and B and use the drawings to carefully check that your models are correct.

27. **T** or **F**: All chiral objects have exactly one enantiomer. If false, cite an example from among A-E.

28. **T** or **F**: All diastereomers are chiral. If false, cite an example from among A-E.

Memorization Task 12.5: Right-Handed and Left-Handed Chiral Centers

A and B (on the previous page) are different (they are enantiomers), so they must have different names.

It turns out that every chiral center can be right handed or left handed. At the end of this activity we will learn how to determine if a chiral center is right or left handed.

The folks who made up this naming system used Latin words for left- and right-handed chiral centers:

- **right**-handed chiral centers are called "**R**" for *rectus,* a Latin word for right, and
- **left**-handed chiral centers are called "**S**" for *sinister,* a Latin word for left.

Model 9: Physical Properties of Enantiomers and Diastereomers

Our right and left hands can be used to model R and S chiral centers, and, as we will see in Model 10, they can even be used to *determine* if a chiral center is R or S.

Demonstration: Making Hand Models

Turn to the person next to you and shake hands with them (right hand to right hand). Each of your **right** hands represents an **R chiral center**, and each of your **left** hands an **S chiral center**. We will therefore call the stereochemistry of the "molecule" you are making by shaking hands the normal way "**R, R**".

Critical Thinking Questions

29. *Keep shaking with your right hands*, but now reach across and simultaneously shake with your left hands (left hand to left hand).
    a. In terms of R and S, how should we name this new "molecule" made with two left hands?
    b. What term describes the relationship between your R,R-handshake and your S,S-handshake?
    c. Identify the external mirror plane between your R,R-handshake and your S,S-handshake.
    d. Note that your handshakes (R,R and S,S) *feel* the same. That is, the S,S-handshake is the same as the R,R-handshake in every way except that it is made from left hands instead of right hands. This represents what we learned in Memorization Task 12.4, that two enantiomers have the same physical properties (e.g. melting point, boiling point, etc.) as one another.

30. **Let go of your partner**. Now offer **one left hand** to be shaken by your **partner's right hand**.
    a. What should we call this new "molecule" in terms of R and S?
    b. What term describes the relationship between an R,S-handshake and the R,R-handshake you made a moment ago? (Note: An R,S-handshake can alternatively be called an S,R-handshake.)
    c. Does your R,S-handshake feel different from an R,R- or S,S-handshake? In what ways?

Addendum to Memorization Task 12.4: Diastereomers have different physical properties

The fact that an R,S- or S,R-handshake feels different from an R,R- or S,S-handshake is supposed to help you remember that diastereomers (e.g., R,S and S,S) have *different* physical properties (mp, etc.)

31. Is your answer to part c of the previous CTQ consistent with the Addendum to Mem. Task 12.4?

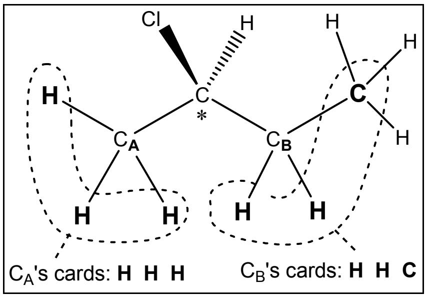
Model 10: Absolute Configuration (Naming Chiral Centers R or S)

The following section describes one way to designate a chiral center R or S (its **absolute configuration**).

There are a number of different systems for assigning R and S. Make sure you learn one and can use it consistently. I like the system described here because, unlike most others, it does not require you to redraw a molecule to determine R or S.

Step 1: Rank the four attached groups 1 (largest) to 4 (smallest)

Use the **Cahn-Ingold-Prelog rules** outlined in ChemActivity 6, Model 11. Recall that priority is assigned based on atomic number with a "card game" system for breaking ties (*see example below)*.

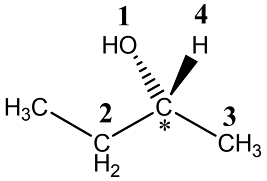


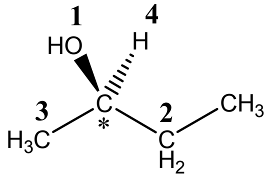
Critical Thinking Questions

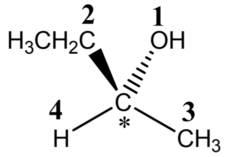
32. Which carbon (C_A or C_B) has a higher rank? Explain your reasoning.

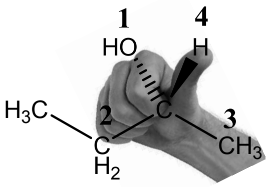
33. Label the four atoms attached to the chiral carbon (*) one to four to show their ranking.

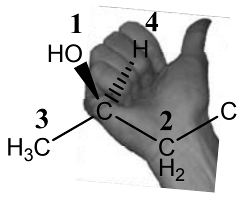
Step 2: Point your RIGHT thumb (hitchhiker style) toward the "4" group (usually an H)

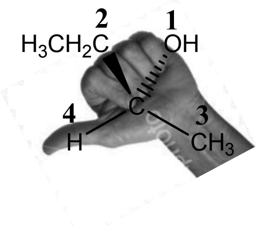












Step 3: Match finger curl (from knuckle to nail) to progression formed by groups 1→2→3

If the curl on your **RIGHT** hand matches the progression from 1→2→3 then the **chiral center is R**.

If curl does not match, **chiral center is S**. Confirm by matching 1→2→3 to finger curl on **LEFT** hand.

Alternatively, touch group 1 with tip of pinky finger then curl pinky to touch group 2, then group 3. Try with both hands. One hand works naturally. The other forces your pinky to bend backwards. If RIGHT hand works → R; if LEFT hand works → S.

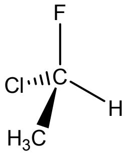
Warning! Don't let your thumb drift. Keep it pointing in the direction of no. 4 (e.g., H) at all times.

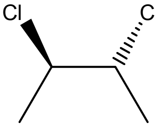
Critical Thinking Questions

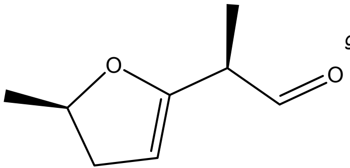
34. Make a model of 2-chlorobutane using the technique shown in the preceding exercise. Identify the "pinwheel" formed by groups 1, 2, and 3, and match the direction of the 1-to-2-to-3 progression to your right or left hand.

35. Determine the absolute configuration of each chiral center on this page, and label each R or S.

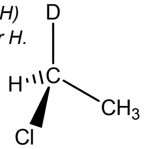
36. Determine the absolute configuration of each chiral center in the following structures.

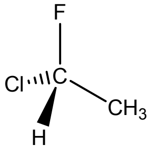


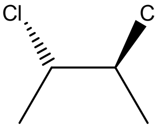


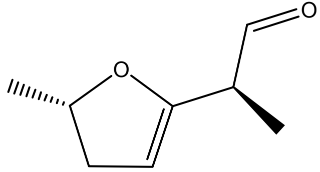


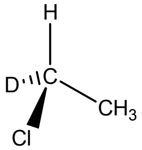
Recall that D (^2H) gets priority over H.











37. Check your work: The structures in the first row are the enantiomers of the structures in the second row. What happens to the absolute configuration of a chiral center if you switch two groups?

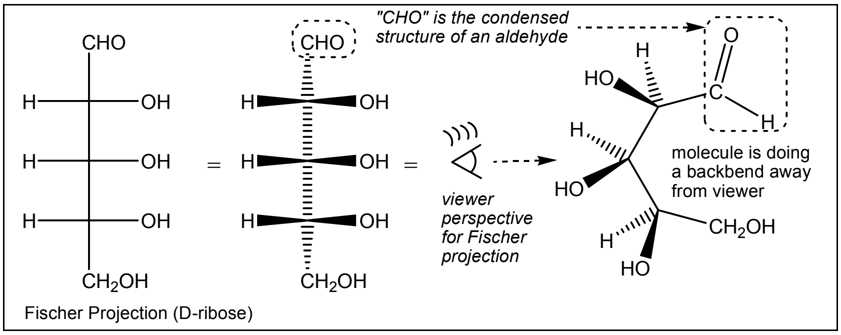
Model 10: Fischer Projections

In a **Fischer projection**, assume:

horizontal bonds = wedge bonds

vertical bonds = dash bonds

The carbon backbone must be drawn vertically with the highest priority group at the top.


CHO
H
OH
H
OH
H
OH
CH_2OH
=
CHO
H
OH
H
OH
H
OH
CH_2OH
=
"CHO" is the condensed structure of an aldehyde
viewer perspective for Fischer projection
O
H
HO
C
H
H
HO
molecule is doing a backbend away from viewer
H
CH_2OH
HO
Fischer Projection (D-ribose)

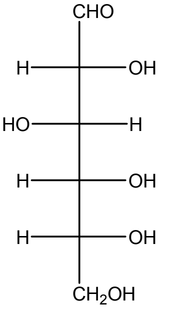
The D/L naming system for sugars is not equivalent to the (+)/(–) or R/S naming systems. A sugar is D if the bottom chiral center on its Fischer projection has an OH to the right, and it is L if that last chiral OH is to the left.

Critical Thinking Questions

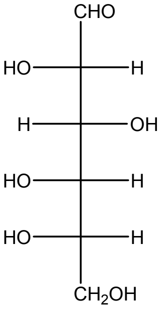
38. Mark each chiral center on the Fischer projection of D-ribose (above) with an R or S.

39. Mark each chiral center on the Fischer projections at right with an R or S.

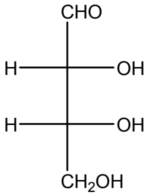
40. How many configurational stereoisomers exist of D-erythrose (including D-erythrose)?



D-glucose



L-glucose



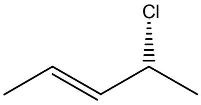
D-erythrose

Memorization Task 12.6: The 2^n Rule

For molecules (except *meso* compounds) the
[no. of configurational stereoisomers] = 2^n
where n = [no. chiral centers] + [no. *E/Z* π bonds]

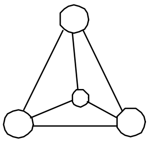
41. How many configurational stereoisomers exist of D-glucose?

42. How many configurational stereoisomers exist for (R,*E*)-4-chloro-2-pentene→ and what are their names?

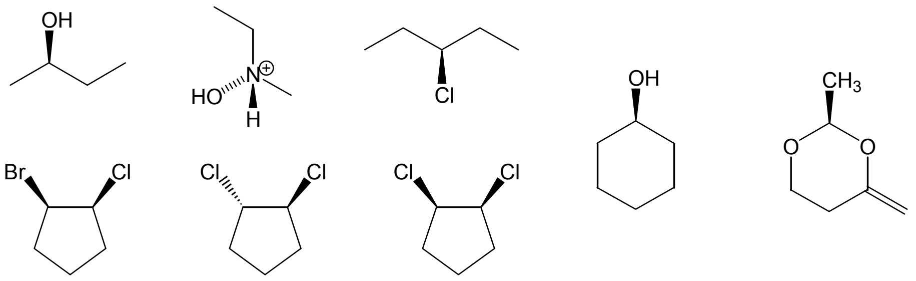


Exercises for Part A:

1. Draw skeletal structures of both configurational stereoisomers of lactic acid (shown in Model 2).
2. Shade or mark the spheres on this object to generate a chiral object.

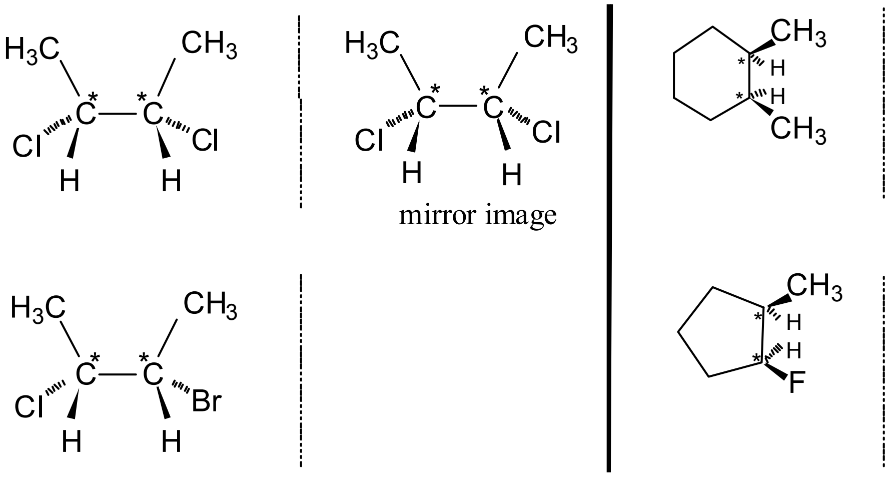


3. Consider the following structures, some of which are chiral.



   a. Label each chiral center with an *. (There are nine chiral centers.)
   b. Circle the **three** structures at the top of the page that are NOT chiral, and for each circled structure, indicate the plane of symmetry (mirror plane).
   c. One of the structures you circled is a *meso* compound. Label it *meso.*

4. Consider the structures below.



   a. Draw the mirror image of each molecule (the first one is done for you.)
   b. Circle the structures that are not chiral, and use a dotted line to show any internal symmetry planes. Label these structures **meso compound**.

5. Read the assigned sections in your text, and do the assigned problems.

Exercises for Part B

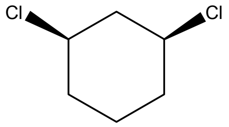
6. Draw an example of a pair of configurational stereoisomers that are NOT enantiomers. What is the name for the relationship between such structures?

7. Draw (–)-tartaric acid next to the structure of (+)-tartaric acid in Model 7.

8. Draw three different configurational stereoisomers of 1,3-dimethylcyclopentane, and label one *meso*.

9. Another quick hand game: Give a partner a R,R-“high five,” and freeze at the point where your palms are touching. (Assume your hands are indistinguishable from your partner’s. That is, ignore differences between your right hand and your partner’s right hand. Assume the same of your left hands.)
    a. Does this R,R “molecule” have an internal mirror plane?
    b. Now make a R,S-high five. Does *this* “molecule” have an internal mirror plane?
    c. Which of these two molecules (R,R-high five, or R,S-high five) is a *meso* compound?
    d. Now simultaneously make S,R and R,S by giving your partner a “high ten,” and confirm that S,R is the same as R,S (The two models can be super-imposed on one another—try it.).

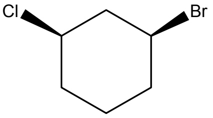
10. A *meso* compound such as the one below can be assigned either R,S or S,R depending on whether you assign the chiral centers from left to right or right to left. So which name is correct? The answer is that both names are logically equivalent and describe the same compound. In fact, the following molecule has four acceptable names, all of them explicit (refer to exactly one molecule). What are the four acceptable names for this molecule?

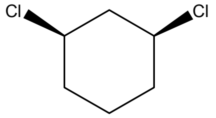


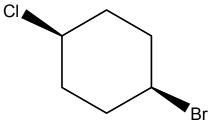
11. There are four possible configurational stereoisomers of 2,3-dichloro**pen**tane. Draw **and name** all four.
    a. There are only *three* possible configurational stereoisomers of 2,3-dichloro**but**ane (two are shown in CTQ 36). Draw the **one** that is missing from CTQ 36, and write its **three acceptable names.**
    b. Explain why there are three stereiosomers in one set and four in the other.

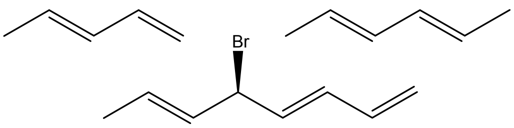
12. The name *cis*-1,3-dichlorocyclohexane is explicit (refers to exactly one molecule), but the name *trans*-1,3-dichlorocyclohexane is not explicit. Explain.

13. How many different configurational stereoisomers exist (including the one shown) for each of the following molecules?





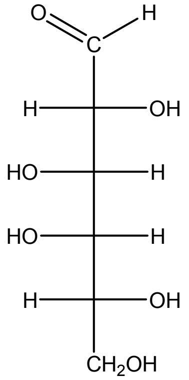


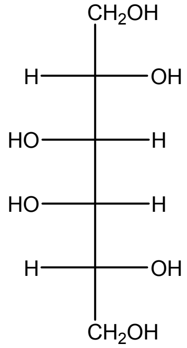


14. Each Fisher projection in Model 10 has a group whose condensed structure is "CHO." What does this group look like if you draw out all the bonds?

15. **Fisher projections** of D-galactose and the reduced form of D-galactose are shown below.

D-galactose





reduced form of
D-galactose

a. Why is it called the "reduced" form of D-galactose?

b. How many chiral centers are there in each molecule?

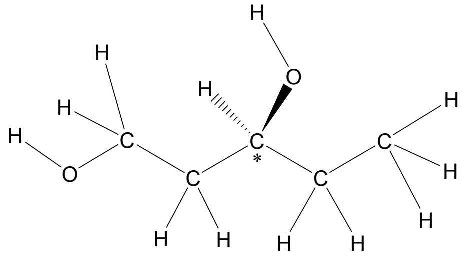
c. How many possible configurational stereoisomers of D-galactose (including D-galactose) are possible?

d. The reduced form of D-galactose has fewer possible configurational stereoisomers. Construct an explanation for why.

e. Specify the stereochemistry of all possible D-galactose configurational stereoisomers (e.g., D-galactose is R,S,S,R).

f. There are only 14 configurational stereoisomers of the reduced form of D-galactose. Specify the stereochemistry of each of these.

16. Sometimes (as in the example at right) the first round of the card game results in a tie. When this happens you must play another round using the next atoms in the chain.

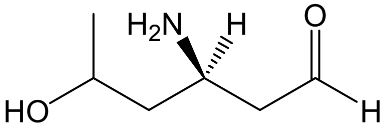


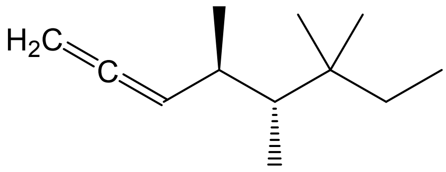
a. Confirm that both C_2 and C_4 hold the same cards, CHH, and therefore tie.

b. Play the card game with the next atoms in the chain to break the tie between C_2 and C_4.

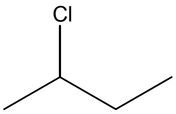
c. Label the four atoms attached to the chiral carbon one to four to show their ranking, and assign R or S.

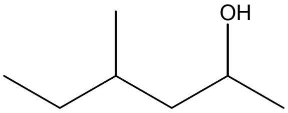
17. Determine the absolute configuration of each chiral center in the following molecules.

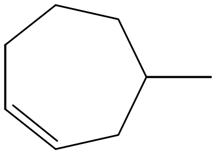




18. Sometimes a molecule with one or more chiral centers is drawn without giving enough information to determine if the chiral center(s) are R or S. Mark each chiral center below with an *.

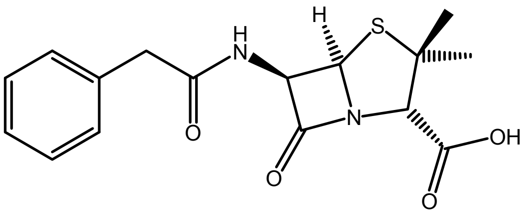




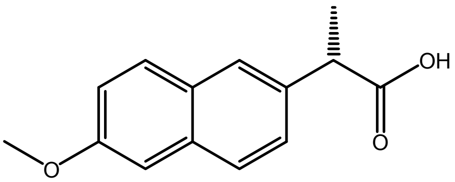


By convention, if enough information is not given to assign R or S, we are to assume that the structure represents an even mixture of all stereochemical possibilities. For each structure above, draw all configurational stereoisomers implied by the drawing.

19. Label every chiral center on the following molecules with an R or S and state whether the molecule as a whole is chiral.



Penicillin G



Aleve (Naproxen)

20. How many different configurational stereoisomers of each molecule in the previous question are there (including the one shown)?

21. Read the assigned sections in your text, and do the assigned problems.

The Big Picture

The immediate purpose of this activity is to refine your skill at seeing molecules in three dimensions. We already have learned reactions that affect the stereochemistry of a molecule (e.g., hydroboration in CA 10), and soon we will be learning more (ChemActivity 13). Seeing and assigning R and S is a critical skill that takes a bit of practice.

The larger purpose of this activity is to introduce you to the complex chiral world around and inside of us. Almost all biological molecules, including interactions between drugs and living systems, are chiral interactions. That is, usually only one configurational stereoisomer of a drug, hormone, protein, or other biomolecule will have the desired effect. In some cases one enantiomer of a drug has therapeutic effects while its mirror image is toxic. This was the case with the anti-nausea drug thalidomide. The R configurational stereoisomer was highly effective and was taken by many pregnant women with debilitating morning sickness. Unfortunately, the S configurational stereoisomer was found (the hard way) to cause terrible birth defects in a large number of mothers who took the drug during gestation.

Ordinary laboratory chemistry is NOT chiral chemistry. That is, when chiral centers are generated, synthetic reactions normally give a racemic mixture of R and S configurational stereoisomers. It is very difficult and expensive for synthetic organic chemists to control the stereochemistry of a reaction and selectively generate one configurational stereoisomer over another. Nevertheless HUGE resources are devoted to this goal because, if the target of the synthesis is related to a biological system (e.g., a drug) the product will not work correctly if it does not have exactly the right absolute configuration at each chiral center.

Common Points of Confusion

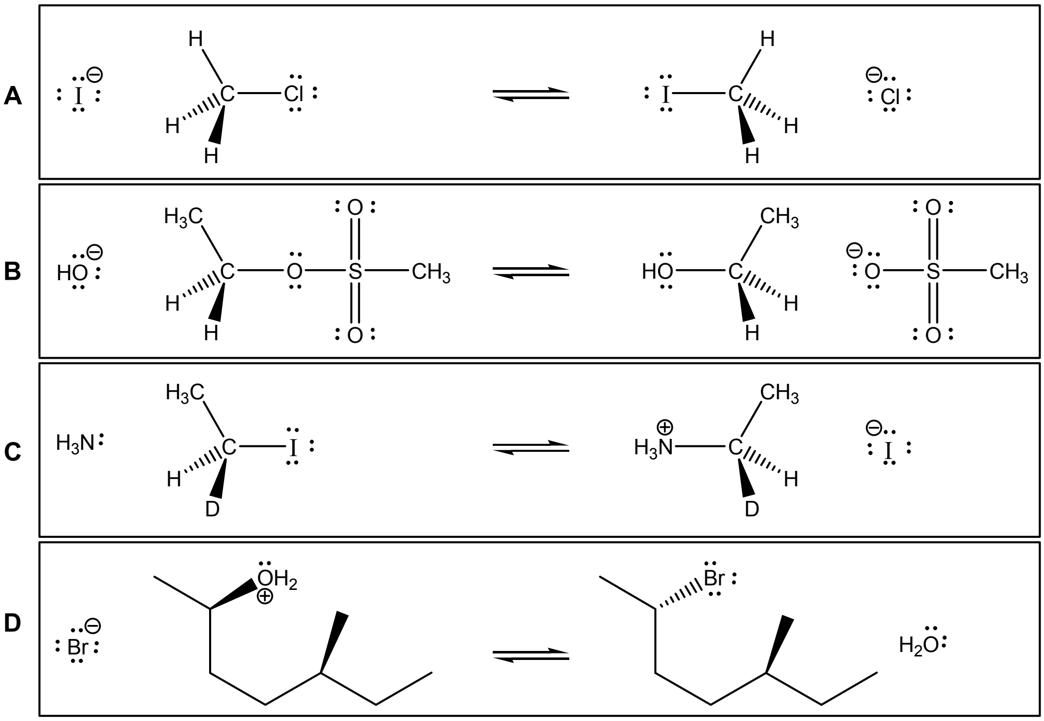
- Another reminder is to watch out for the term "**stereoisomer**" used by itself. In many places and in many textbooks this term is used in place of the term "**configurational stereoisomer**." (Recall that configurational stereoisomers are the *E/Z, cis/trans*, **R/S, D/L, +/-** enantiomers, diastereomers, etc. that we have been working with in this ChemActivity.) The strictly correct use of the term "stereoisomer" includes all stereoisomers. That is, both configurational stereoisomers and conformational stereoisomers (conformers—covered in ChemActivity 6A).
- The definitions in this activity cause some confusion. Enantiomer is not so bad once you realize it is just another word for mirror image if you are talking about a chiral molecule. Students have more trouble with **diastereomer**. It may help to think of diastereomer as the "catch all" configurational stereoisomer term. If two molecules have the same connectivity, but do not fall into any other category (conformer/same or enantiomer), then they are diastereomers.
- Students tend to get caught up in the chirality issue and overlook the fact that a pair of *cis/trans* or *E/Z* configurational stereoisomers are diastereomers of each other **even if they are not chiral!**
- All students struggle with assigning R/S. Students who are persistent in working with both a model and pencil/paper eventually can assign R and S with a high degree of accuracy. There are three main types of difficulties: **1)** Errors assigning priorities [*Remedy*: Review the rules in ChemActivity 6.], **2)** difficulty seeing the chiral center in 3D [*Remedy*: Work with a model and a drawing at the same time.], and **3)** Mixing up different numbering systems or methods of assigning R and S [*Remedy*: Invest in one method. They all work, but learning more than one causes confusion.].
- When counting isomers it is tempting to use the **2^n rule** without thinking. You must be mindful of symmetrical molecules with the possibility for *meso* compounds among the configurational stereoisomers.

ChemActivity 13: Substitution

PART A: ONE-STEP NUCLEOPHILIC SUBSTITUTION

(What is the mechanism of an S_N2 reaction?)

Model 1: Examples of One-Step Nucleophilic Substitution Reactions



Critical Thinking Questions

1. In each reaction in Model 1, an “incoming group” displaces (*substitutes for*) a “**leaving group**.”
   a. (E) Circle each “incoming group” among the reactants in Model 1.
   b. (E) Put a box around each leaving group among the reactants in Model 1.
   c. (E) Can leaving groups and incoming groups consist of more than one atom?
   d. (E) **True or False**: an incoming group must be negatively charged.
   e. **True or False**: a neutral leaving group will be negatively charged after it leaves, and a positively charged leaving group will be neutral after it leaves.

2. Add a δ+ to the most electrophilic (electron loving) carbon among each set of reactants, and label the molecule containing this **electrophilic carbon** the “**electrophile.**”
3. Use curved arrows to illustrate a one-step mechanism that will accomplish each substitution reaction in Model 1. (*Hint*: You will need to draw more than one arrow for each reaction.)
4. Label the species among the reactants that is acting as a **nucleophile** (nucleus loving).

Memorization Task 13.1 (Check your work): Nucleophile, Electrophile and Leaving Group

In a nucleophilic substitution reaction the participants are commonly referred to by the following names:

- **nucleophile** = incoming group
- **electrophile** = species containing the **electrophilic carbon**
- **leaving group** = leaving group

Model 2: Transition State

The **transition state (t.s.)** of a reaction is the highest potential energy species between the reactant and the product. The diagram below shows two possible transition states for Reaction A in Model 1.

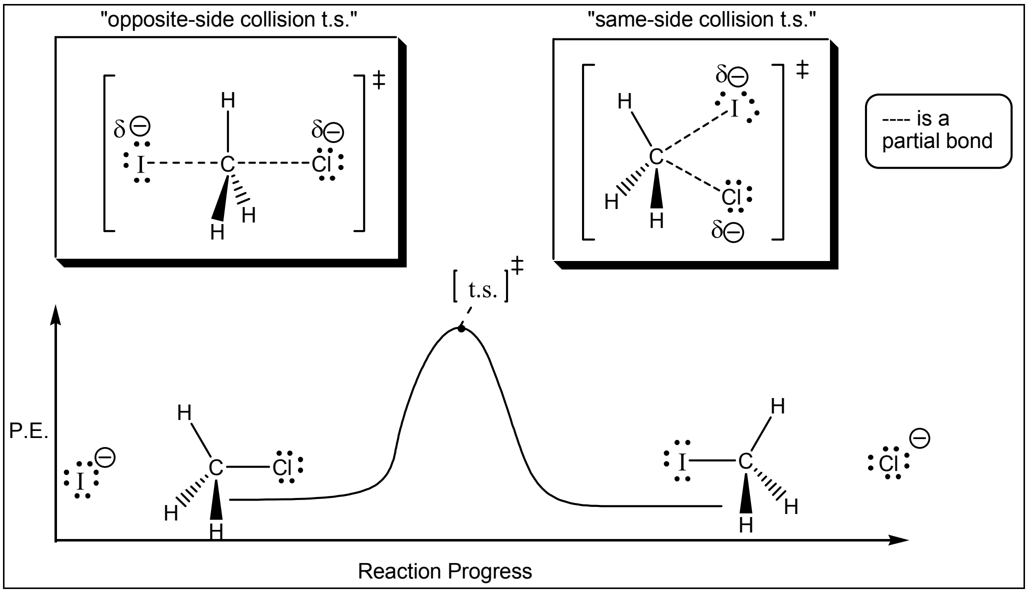


Figure 13.1: Two possible transition states for a one-step nucleophilic substitution reaction

Critical Thinking Questions

5. Assign an R or S to each chiral center (reactants and products) among Reactions A-D in Model 1.
6. Explain why the data in Model 1 (specifically, Reactions C and D) support the opposite-side collision transition-state hypothesis.
7. Same-side collision does not occur. (Cross out this transition state in Model 2.) If one-step nucleophilic substitution reactions did proceed via a same-side collision, what would be the absolute configurations (R or S) of the chiral centers in the products of Reactions C and D?
8. Explain why, in Reaction D, the absolute configuration of C_5 does not change during the reaction.

Model 3a: Rate-Limiting Step (for leaky buckets)

Consider the rate of water flow through the following series of buckets with differently sized holes.

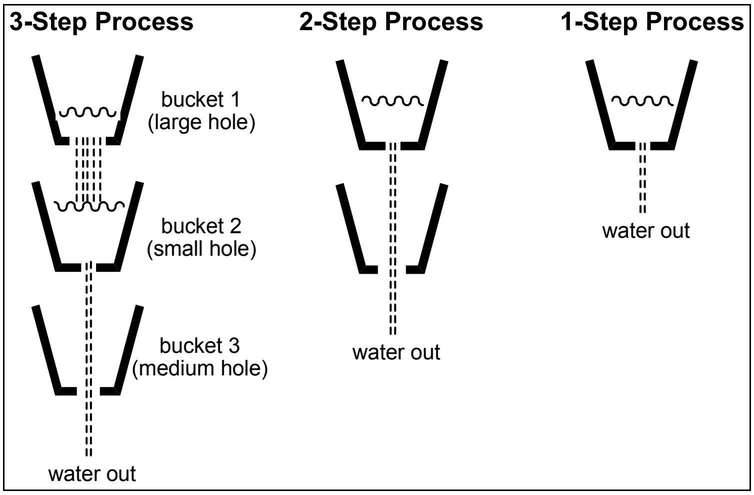


Figure 13.2: Rate-limiting step as illustrated by leaky buckets

Critical Thinking Questions

9. Does the rate of water flow in the Three-Step Process **increase, decrease,** or **stay the same** when you increase the size of the hole in …
   a. bucket 1?
   b. bucket 2?
   c. bucket 3?

10. Identify the slowest step (the **rate-limiting step**) in each process in Model 3a.

Model 3b: Rate-Limiting Step (for reactions)

Like the bucket processes, every reaction has a slowest step. This is called the **rate-limiting step** or **rate-determining step**. For reactions, the slowest step is the step with the highest-energy transition state.

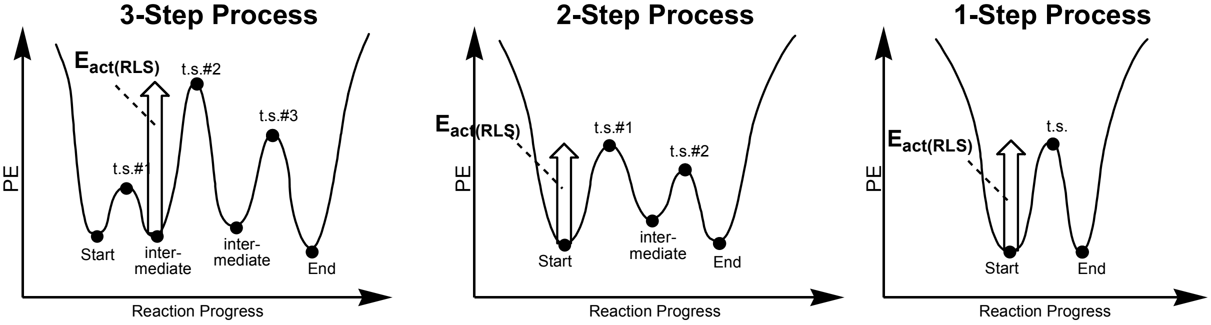


Figure 13.3: Energy diagrams of hypothetical three, two, and one-step reactions

Reactions happen when reactant molecules collide in solution. The temperature of a solution essentially tells you how fast the molecules are going, and $E_{act(RLS)}$ tells you how fast they *need* to be going in order to react. But **how often do they collide?** This largely depends on how many **solvent** molecules are around to get in the way. In other words, the **collision rate** is a function of how many solvent molecules there are in comparison to reactant molecules. This ratio is called **concentration** (usually in moles/L).

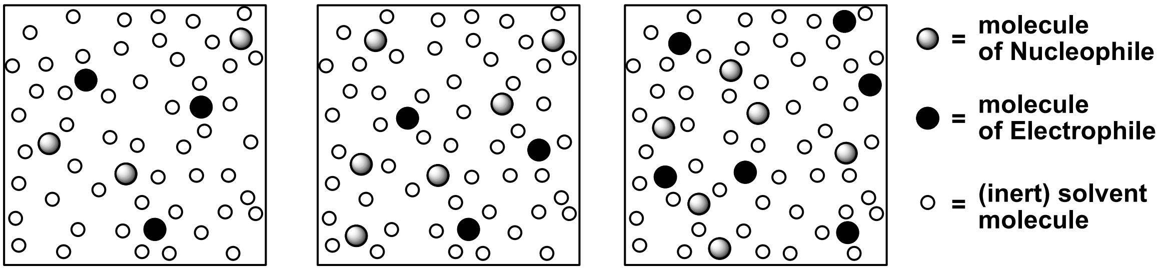

= molecule of Nucleophile
● = molecule of Electrophile
○ = (inert) solvent molecule

Figure 13.4: Cartoons showing low-, medium-, and high-concentration solutions

Critical Thinking Questions

11. Identify the rate-limiting step for each energy diagram in Figure 13.3.

12. Which energy diagram in Figure 13.3 is most likely to be a one-step nucleophilic substitution?

13. Construct an explanation for why the rate of the reaction shown in the far right box in Figure 13.4 is two times that of the middle box and four times that of the far left box.

Memorization Task 13.2: Rate Expression

The **rate expression** is an equation relating the rate of a reaction (as measured by the appearance of product) to concentration. The rate of a reaction changes when you change the concentration of a species involved in the slowest step, so only species involved in the slow step appear in the rate expression.

Reactions in Model 1 have only one step, so this must be the slowest step, and the **rate expression** is…

rate = *k* x [nucleophile] x [electrophile]

(where *k* is an experimentally determined constant called the **rate constant**)

Critical Thinking Questions

14. (E) Write the rate expression for Reaction A in Model 1.

15. What is the effect on the rate of Reaction A of doubling both $[I^-]$ and $[CH_3Cl]$?

Term Introduction: One-step Nucleophilic Substitution Reaction = "S_N2 Reaction"

- **S** stands for **S**ubstitution
- **N** stands for **N**ucleophilic
- **2** stands for bimolecular (**two** molecules involved in the rate-determining step)

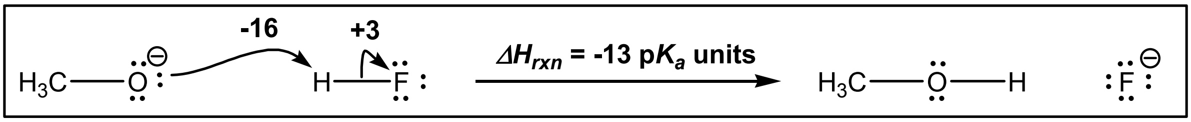
Note: If this terminology seems backwards, just you wait! In Part C of this activity we will encounter *two*-step nucleophilic substitution reactions, which (of course) are called "**S_N1 reactions**."

Summary: $S_N\underline{2}$ reactions are one-step while $S_N\underline{1}$ reactions are two-step. Just remember that the "1" and "2" in S_N1 and S_N2 refer to the number of species in the slowest step (*NOT the number of steps*).

PART B: USING pK_a TO PREDICT S_N2 REACTION OUTCOMES

(What are the characteristics of a favorable S_N2 reaction?)

Model 4: Review of Acid-Base Reactions and pK_a



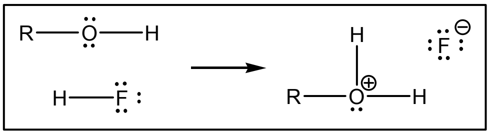
pK_a of HF = 3 **pK_a of CH_3OH = 16**

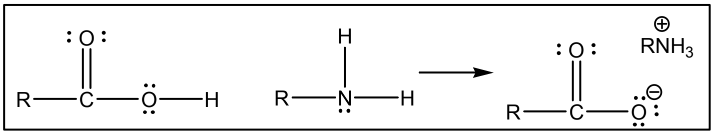
Review: Making a bond releases (–) energy. *[By convention this energy is given a negative sign.]*

Breaking a bond requires input of (+) energy. *[By convention this energy is given a positive sign.]*

Critical Thinking Questions

16. (Review) Explain how the value of $\Delta H_{rxn} = -13$ pK_a units was calculated for the reaction above.
17. (Review) Use curved arrows to show the mechanisms of the following two acid-base reactions.





a. (Review) Above each curved arrow write a positive or negative number that gives the energy change associated with that arrow. (Use the pK_a table on the inside back cover of this book, and assume that the pK_a of a strong acid is zero.)

b. (Review) Calculate ΔH_{rxn} in pK_a units, and write this value above each reaction arrow.

18. Proton transfer reactions such as the ones above are mechanistically identical to S_N2 reactions. By analogy with S_N2, identify the **nucleophile, electrophilic atom,** and **leaving group** for each.
19. Label each reaction on this page favorable (downhill) or unfavorable (uphill).

20. Consider the H—LG bond (LG = Leaving Group)

a. In a favorable (downhill) S_N2 reaction, this bond is **easy** or **hard** (circle one) to break?

b. In a favorable (downhill) S_N2 reaction, the pK_a associated with the H—LG bond is **low** or **high** (circle one)? Explain your reasoning.

21. Consider the formation of a the new Nuc—H bond (Nuc = Nucleophile)

a. For a favorable (downhill) S_N2 reaction, this bond should be **weak** or **strong** (circle one)?

b. For a favorable (downhill) S_N2 reaction, the pK_a associated with the newly formed Nuc—H bond should be **low** or **high** (circle one)? Explain your reasoning.

Term Introduction

good leaving group → makes S_N2 reaction more favorable; **poor leaving group** → S_N2 less favorable

good nucleophile → makes S_N2 reaction more favorable; **poor nucleophile** → S_N2 less favorable

*For now, you can interpret "favorable" as meaning "downhill/exothermic." Such reactions are called **thermodynamically favorable**. (pK_a data tell you if an acid-base reaction is thermodynamically favorable.) Later we will discuss reactions that are downhill (thermodynamically favorable), but still do not produce products because they are too slow (kinetically unfavorable).*

Model 5: Using the pK_a of an H—Z Bond to Analyze a C—Z Bond

Strictly interpreted, pK_a values give the energy required for polar breakage of an H—Z bond in water. However, similarities between C and H allow us to extend the concept of pK_a and apply it to C—Z bonds.

That is, the pK_a's of two molecules (H—Z_1 and H—Z_2) can be used to estimate the relative amounts of…

- **(+) energy required to break a C—Z_1 bond,** as compared to a C—Z_2 bond
- **(–) energy released when a C—Z_1 bond is formed,** as compared to a C—Z_2 bond.

For example:

Fact based on pK_a data: It is easier to break an $H{-}\overset{\oplus}{O}R_2$ bond than an $H{-}OR$ bond.

Conclusion 1: It is easier to break a $C{-}\overset{\oplus}{O}R_2$ bond than a $C{-}OR$ bond.

Conclusion 2: OR_2 is a better leaving group than $^{\ominus}OR$

Fact based on pK_a data: Formation of an $H{-}OR$ bond releases more energy than formation of an $H{-}\overset{\oplus}{O}R_2$ bond

Conclusion 1: Formation of a $C{-}OR$ bond releases more energy than formation of a $C{-}\overset{\oplus}{O}R_2$ bond

Conclusion 2: $^{\ominus}OR$ is a better nucleophile than OR_2

Critical Thinking Questions

22. According to the "**C is like H assumption**" in Model 5, about how many pK_a units of energy…

    a. does it take to break a $C{-}\overset{\oplus}{O}R_2$ bond?

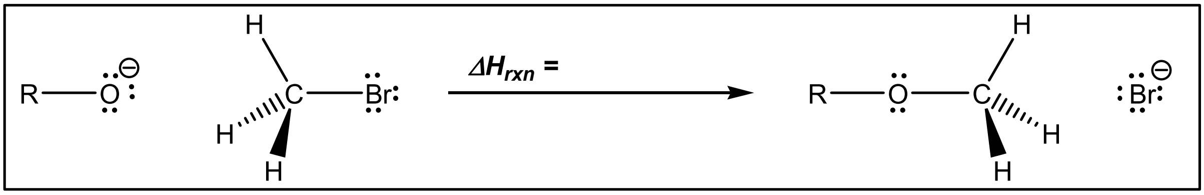
    b. does it take to break a C—OR bond?

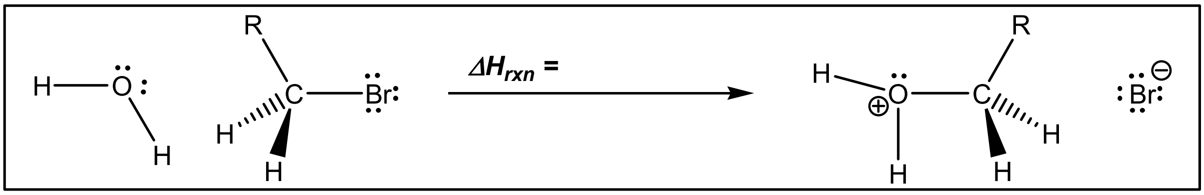
    c. are released when $^{\ominus}$ OR combines with C to make a new C—OR bond?

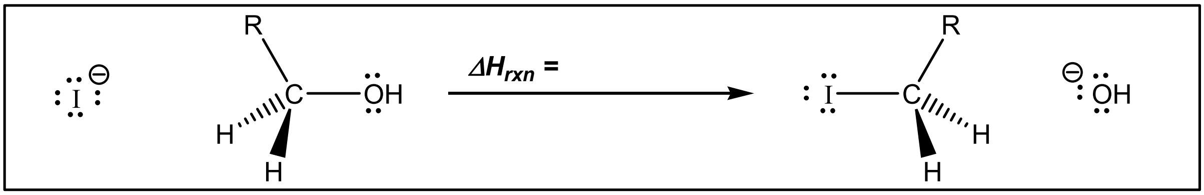
    d. are released when OR_2 combines with C to make a new $C{-}\overset{\oplus}{O}R_2$ bond?

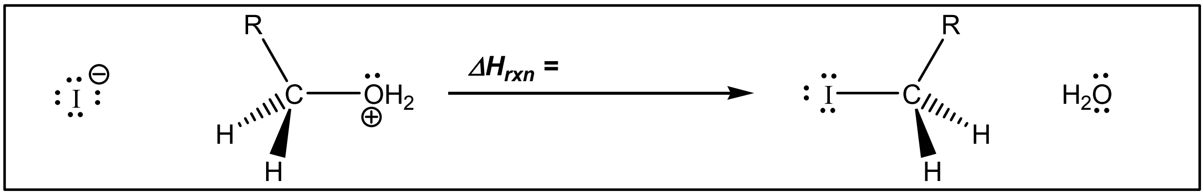
23. Explain how your answers to a through d in the previous question support the conclusions in Model 5.

24. Add curved arrows to each of the following S_N2 reactions. Label each arrow with an energy change, and calculate an estimated ΔH_{rxn} in pK_a units (based on H—Z pK_a values).



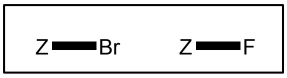


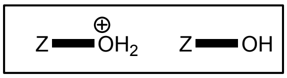


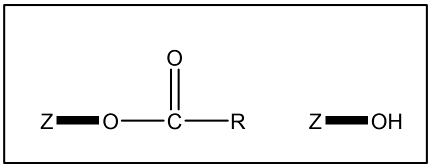


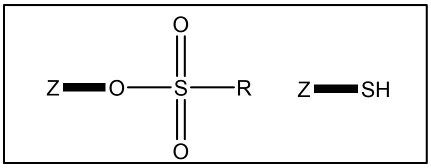
25. Write "No Reaction" next to the one reaction in the previous question that is very unlikely to produce the products shown.

26. For each pair, circle the better leaving group (assume breakage of the bond highlighted in **bold**).

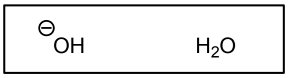


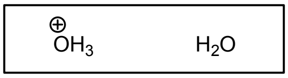


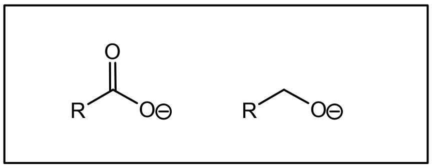


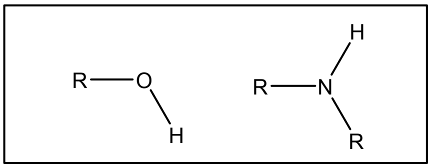


27. For each pair, circle the better nucleophile (based on the pK_a data at the back of this workbook).









Memorization Task 13.3: Leaving Groups (table) and Nucleophiles (table)

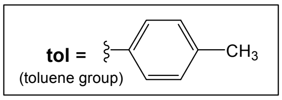
R = H or alkyl

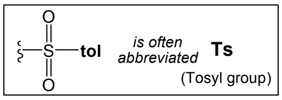
Very Good Leaving Groups	Good Leaving Groups	Poor Leaving Groups
RSO_3^- *(most often… R= CF_3, R= tol, or R= CH_3)* I^-	R_2O *(water, alcohol, or ether)* Br^- Cl^-	F^- *strong bases are very poor leaving groups* RO^- R_2N^- R_3C^-

Table 13.1: Common Leaving Groups

Very Good Nucleophiles	Good Nucleophiles	Poor Nucleophiles
RS^- NC^- I^- PR_3 $*R_3C^-$ $*R_2N^-$ $*RC{\equiv}C^-$ $*RO^-$	Br^- R_2S NR_3 Cl^- RCO_2^- N_3^-	F^- HCO_3^- R_2O *(water, alcohol, or ether)* *All strong acids are very poor nucleophiles*

Table 13.2: Common Nucleophiles





**These nucleophiles are also strong bases. They will NOT undergo S_N2 reactions when there is a faster acid-base pathway available (more on this later).*

Critical Thinking Questions

28. (Check your work) Are your answers to the two CTQ's at the bottom of the previous page consistent with the Tables above?

29. Next to each leaving group in Table 13.1, write the pK_a of its conjugate acid. (Write "0" next to the conjugate base of any strong acid.)

30. Except for F^-, leaving group trends in Table 13.1 exactly follow predictions based on pK_a data. Nucleophile strength also follows pK_a, but there are some important exceptions. Cite at least four species in Table 13.2 that are expected to be poor nucleophiles based on pK_a data, but instead are good or very good nucleophiles.

Memorization Task 13.4: I^-, Br^- & Cl^- are unexpectedly good nucleophiles (a.k.a. "soft")

The explanation for this stems from the fact that the third-, fourth-, and fifth-row halide ions (I^-, Br^- and Cl^-) have big "fluffy" polarizable orbitals that can stretch out and begin to make a bond to the electrophilic carbon from far away, leading to lower P.E. transition states and faster S_N2 reactions. I^-, Br^- and Cl^- are therefore called "**soft nucleophiles**" while F^- is an example of a "**hard nucleophile**."

Memorization Task 13.5: Nucleophilicity increases as you go down the periodic table.

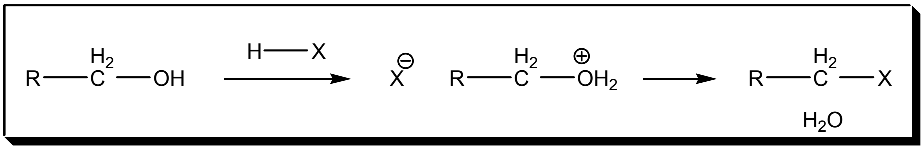
The trends described above for halogens are also true for elements in other columns of the periodic table.

Critical Thinking Question

31. Cite a pair of nucleophiles from Table 13.2 that illustrate the **periodic trend** described in Memorization Task 13.5.

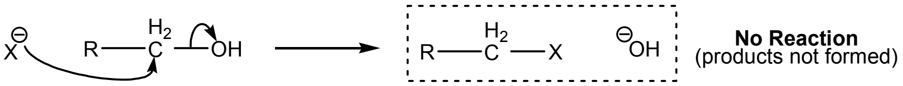
Synthetic Transformation 13.1: Halogenation of an Alcohol using HX (X = Cl, Br, or I)

13.1



Critical Thinking Question

32. Add curved arrows to show the mechanism of both **mechanistic steps** in Synth. Transf. 13.1.
    a. What is the pK_a of the conjugate acid of hydroxide (HO$^-$)?
    b. Explain why the following reaction does NOT work.



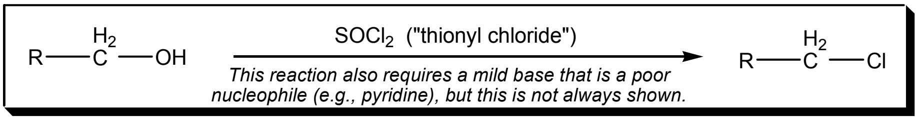
No Reaction
(products not formed)

    c. An acid can transform the OH of an alcohol (R—OH) from a terrible leaving group into an excellent one. What is this excellent leaving group, and what is the pK_a of its conjugate acid?

Synthetic Transformations 13.2 and 13.3: Halogenation of an Alcohol using $SOCl_2$ or PBr_3

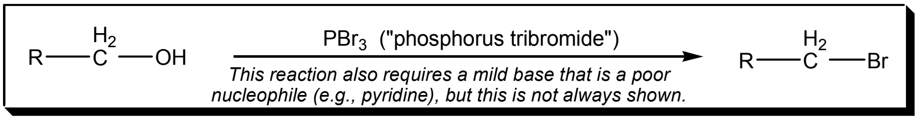
In this course we will **commonly transform OH of R—OH into an excellent leaving group using acid**, as shown in the first step above. However, the second step above does not always work. In practice such transformations are often carried out by a different mechanism using $SOCl_2$ or PBr_3 (shown below).

13.2



This reaction also requires a mild base that is a poor nucleophile (e.g., pyridine), but this is not always shown.

13.3

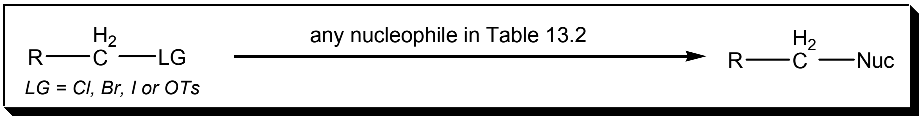


This reaction also requires a mild base that is a poor nucleophile (e.g., pyridine), but this is not always shown.

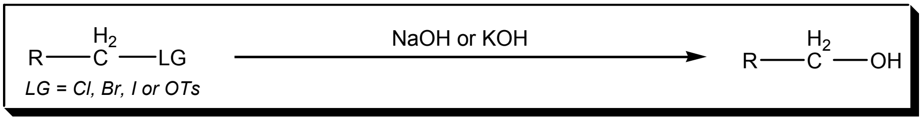
Synthetic Transformations 13.4a-d: Examples of Synthetic Uses of S_N2 Reactions

Almost any leaving group from Table 13.1 can be replaced with a nucleophile from Table 13.2.

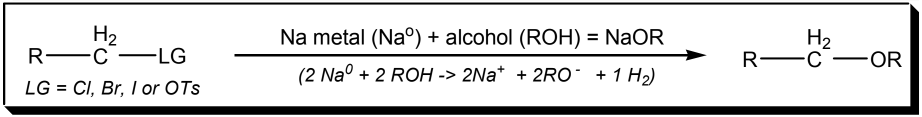
13.4a



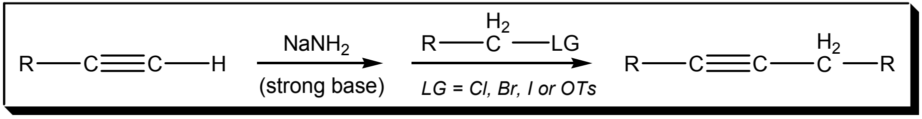
13.4b



13.4c


R—CH2—LG
Na metal (Na°) + alcohol (ROH) = NaOR
(2 Na0 + 2 ROH -> 2Na+ + 2RO- + 1 H2)
R—CH2—OR
LG = Cl, Br, I or OTs

13.4d



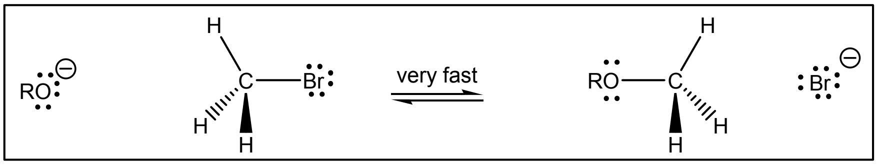
PART C: SUBSTITION AT 2^{o} AND 3^{o} ELECTROPHILIC CARBONS

(How can we explain nucleophilic substitution reactions at tertiary carbons?)

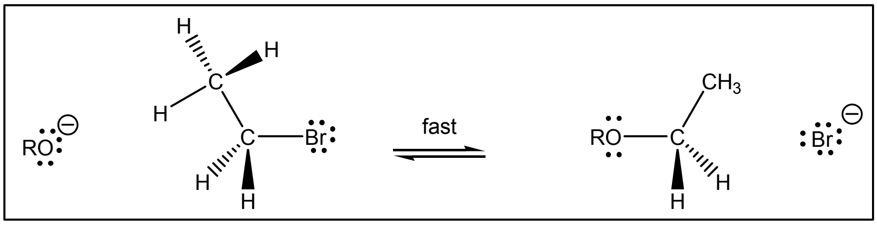
Model 6: S_N2 Reactions that are Downhill but Slow

The four reactions below share the same nucleophile and leaving group, and each is steeply downhill based on p*K*$_a$ data (ΔH = -16 pK_a units). Yet they have very different **S_N2 reaction rates**.

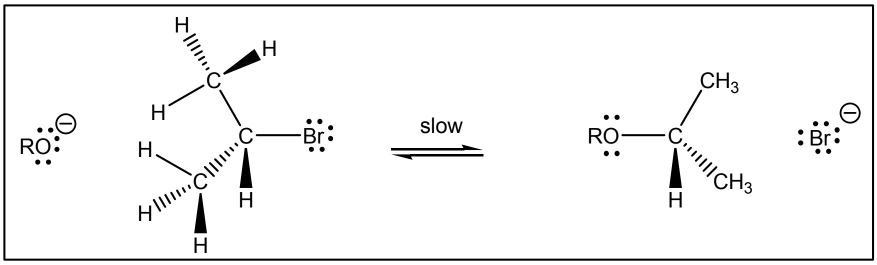
I



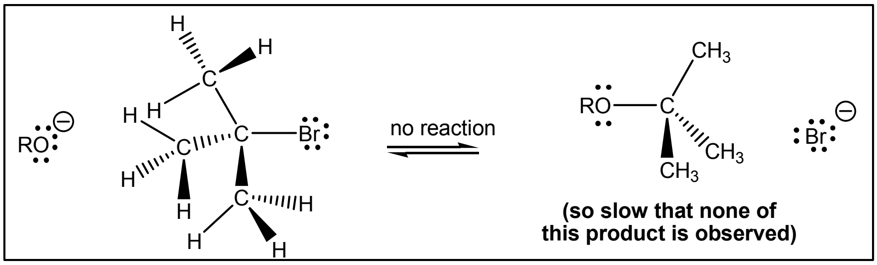
II



III



IV



Critical Thinking Questions

33. Add curved arrows to each reaction in Model 6 showing an S_N2 reaction.

34. Label each electrophilic C in Model 6 as methyl (0^{o}), primary (1^{o}), secondary (2^{o}) or tertiary (3^{o}).

35. Construct an explanation for why…

    a. **Reaction IV** is slower than **Reaction III; Reaction III** is slower then **Reaction II**; etc.

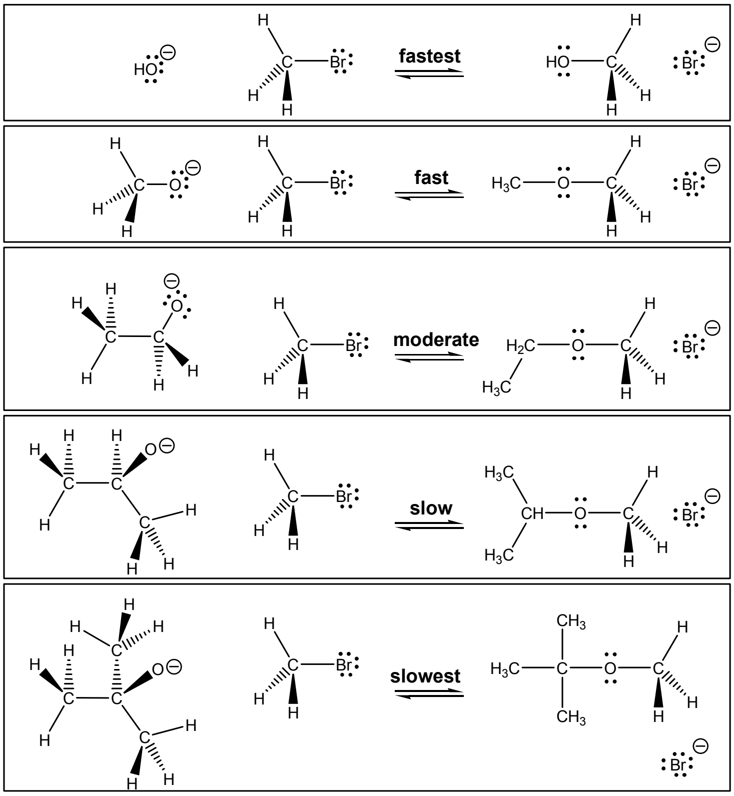
    b. For a given reaction (**I to IV**), the rate is slower when R = CH_3 than when R = H.

36. Which reaction from Model 6 (previous page) is shown at right with five different nucleophiles?

a. The nucleophile in Reaction I (on the previous page) is RO^{-}. At right, the "R" group is specified. Describe how "R" differs from top to bottom.

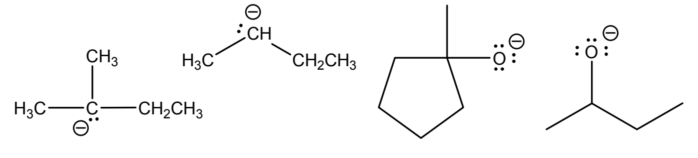
b. Explain why, when R = ethyl (at right) the rate is slower than when R = methyl.

c. Explain why the rate is slowest when the nucleophile is *tert*-butoxide (R = *tert*-butyl).



Memorization Task 13.6: Nucleophiles, definitions of large and small

For simplicity, we will use the following definitions of small and large nucleophiles:

Definition	*Examples:*
Small single atom, methyl, or primary but not next to a branch point	$:H^{\ominus}$ $HO^{\ominus}$ $H_3C{-}O^{\ominus}$ $H_3C{-}CH_2{-}O^{\ominus}$ $:Br:^{\ominus}$ $H_2O:$ $H_3C{-}NH_2$ $H_3C:^{\ominus}$
Large tertiary, secondary, or primary next to a branch point (attached directly to a 2° or 3° atom)	

Critical Thinking Question

37. Characterize each nucleophile at the top of this page as small or large.

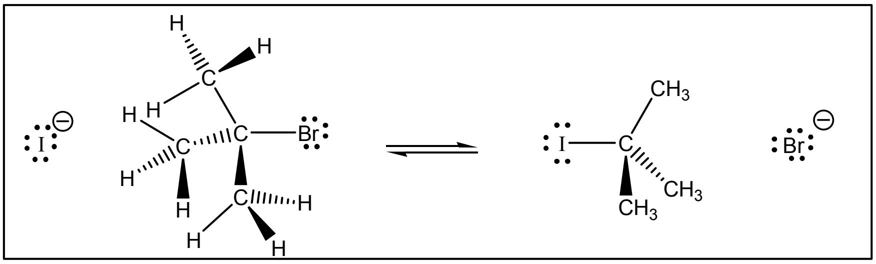
Memorization Task 13.7: S_N2 fastest with [small Nuc] & [methyl or 1° electrophilic carbon]

- Secondary (unbranched) electrophilic carbons can undergo S_N2 with a *small* nucleophile.
- Tertiary electrophilic carbons DO NOT undergo S_N2 with any nucleophiles.

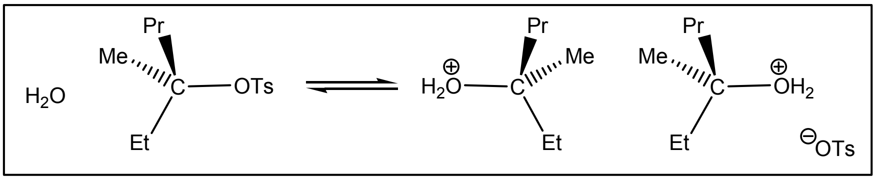
Model 7: Two-Step Nucleophilic Substitution (S_N1) Reactions

It turns out that substitutions *can* occur at secondary or tertiary electrophilic carbons, just not by an S_N2 mechanism. Each pair of reactants below undergoes a two-step substitution mechanism called **S_N1**.

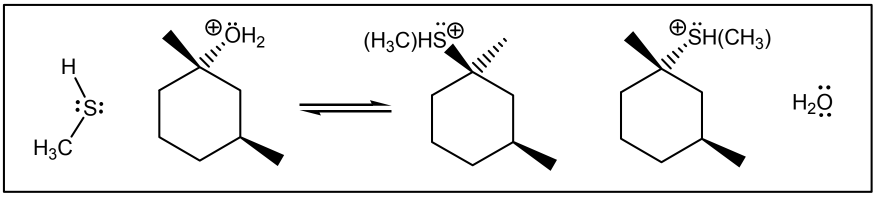
V



VI



VII

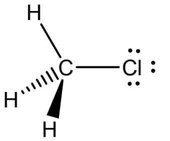


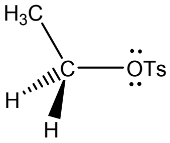
Critical Thinking Questions

38. In the first step of an S_N1 reaction, the leaving group leaves, giving a carbocation intermediate. Based on this information, use curved arrows to illustrate the mechanism of **Reaction V** from Model 7. **Be sure to draw the carbocation intermediate.**

39. The reactants in Model 7 cannot undergo a one-step nucleophilic substitution (S_N2) because the resulting transition states would be too crowded. How is this overcrowding problem attenuated (made smaller) in the first step of an S_N1 mechanism?

40. Sketch the carbocations that would result *if* the following electrophiles were to undergo S_N1 reactions (*though they do not undergo S_N1*).





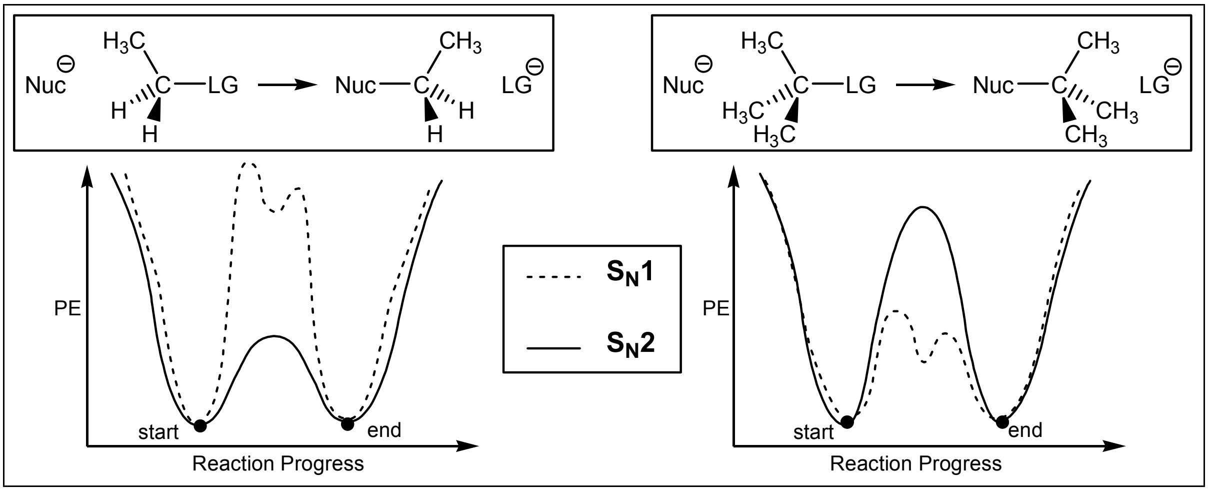
a. Label the carbocations you drew above and the carbocation in your mechanism on the previous page as methyl (0°), primary (1°), secondary (2°) or tertiary (3°) as appropriate.

b. (Review) Rank the carbocations that you labeled from most favorable (most likely to form) to least favorable (least likely to form).

c. Construct an explanation for why the pairs of reactants in *this* question DO NOT undergo S_N1 reactions while those in **Reactions V to VII** (on the previous page) do undergo S_N1.

41. Mark the point on each S_N1 reaction pathway below that represents the carbocation intermediate. Mark one of these points, **"1°/too high PE to form"** and the other point **"3°/very likely to form."**

Model 8: S_N1 vs. S_N2 at a 1° vs. 3° Electrophilic Carbon



Critical Thinking Questions

42. According to Model 8, which step (first or second) is rate-determining in an S_N1 reaction?

43. Use this information to write a possible rate expression for an S_N1 reaction. (See Mem. Task 13.2.)

44. Will changing the concentration of the nucleophile change the rate of an S_N1 reaction? Explain why or why not.

45. (Check your work) Is your answer to the previous question consistent with the following rate data?

Nucleophile e.g., I^-	**Electrophile—LG** e.g., $(CH_3)_3C—Br$	**Relative Reaction Rate**
1 M	1 M	1
2 M	1 M	1
1 M	2 M	2
2 M	2 M	2

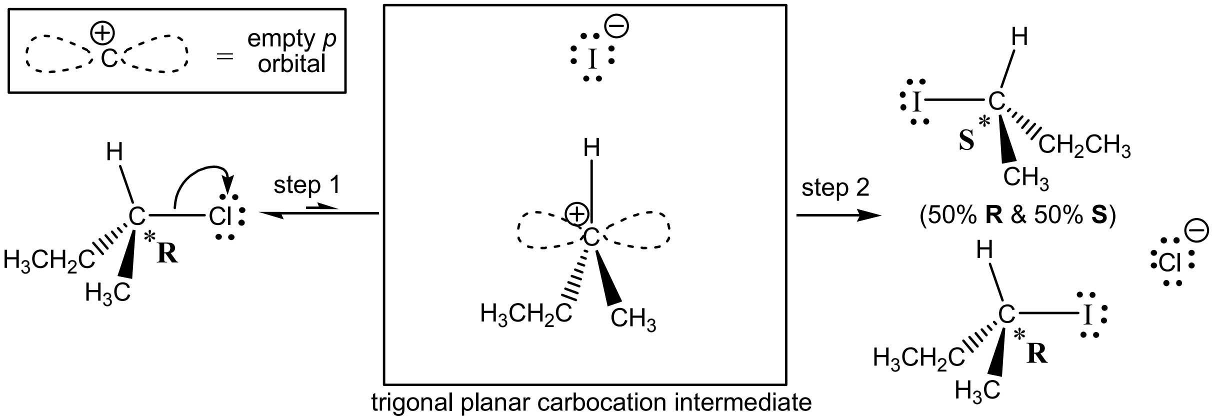
Table 13.3: Effect of concentration on rate for S_N1 reaction

46. (Review) Explain why a two-step nucleophilic substitution reaction is called an $S_N\underline{1}$ reaction. What does the "1" stand for (if not the number of steps)?

47. Consider the S_N1 reaction below:

    a. Add a curved arrow to illustrate how the **S** product could be generated in step 2 of this reaction, and label this arrow "**S-forming**."

    b. Draw a second curved arrow showing how the **R** product is formed and label it "**R-forming**."



48. Explain why an S_N1 reaction at a chiral electrophilic carbon does NOT lead to chiral inversion the way an S_N2 reaction at a chiral center is known to do.

49. What is the special name of a 1:1 mixture of enantiomers like the product mixture produced in the reaction above (and in **Reaction VI** of Model 7)?

PART D: FACTORS AFFECTING S_N1 vs. S_N2

(What reagents are more likely to undergo S_N1 versus S_N2?)

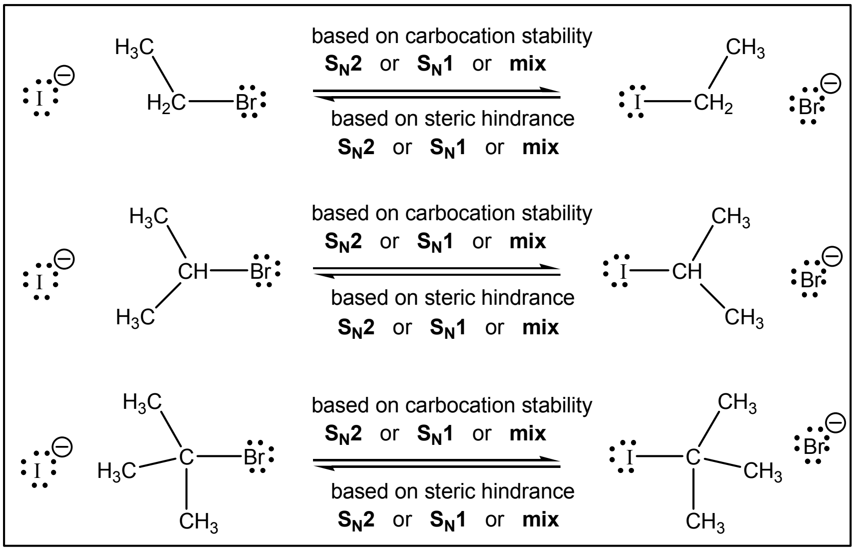
Model 9: S_N1, S_N2 or a Mixture of the Two?

- One pair of reactants in the box below goes to products exclusively by an S_N2 mechanism.
- One pair goes exclusively by an S_N1 mechanism.
- One pair goes by a mixture of S_N1 and S_N2 mechanisms.

Reaction 1

Reaction 2

Reaction 3



Critical Thinking Questions

50. Which alkyl bromide CANNOT form a favorable carbocation? Cross out "S_N1" and "mix" ABOVE the reaction arrow for this reaction to indicate that S_N1 cannot occur.

51. Which alkyl bromide will form the lowest potential energy (most favorable) carbocation when Br leaves? Circle "S_N1" above the appropriate reaction arrow to show that S_N1 is favorable.

52. Which alkyl bromide is least crowded and so MOST likely to proceed via a one-step (S_N2) mechanism? Circle "S_N2" below the appropriate reaction arrow.

53. Which alkyl bromide is too crowded to proceed via a one-step (S_N2) mechanism? Cross out "S_N2" and "mix" below the appropriate reaction arrow.

54. Fill in each of the blanks in the following summary sentences with either "**S_N1**" or "**S_N2.**"

    a. Reaction 1 in Model 9 must proceed via an _____ mechanism. It cannot undergo _____ because it would have to form a very unfavorable carbocation. Conveniently, it turns out to be perfect for _____ because the electrophile is so uncrowded.

    b. Reaction 3 in Model 9 must proceed via an _____ mechanism. It cannot undergo _____ because the transition state would be too crowded. Conveniently it turns out to be perfect for _____ because the electrophile forms a very favorable carbocation when Br leaves.

Term Introduction: Steric Factors vs. Electronic Factors

steric factors = factors having to do with overcrowding (forcing atoms to be too close together)

electronic factors = factors having to do with where the electrons are found (e.g., electronegativity, resonance, hybridization, or inductive effects)

Critical Thinking Question

55. When it comes to deciding whether a reaction will be S_N1 or S_N2, are **electronic factors (carbocation stability)** and **steric factors** in agreement or in competition? Explain.

Check your work:

Based on both steric and electronic (carbocation stability) factors, Reaction 2 in Model 9 is expected to be a mix of S_N1 and S_N2. Therefore, circle "mix" above and below this reaction arrow in Model 9.

Model 10: Solvent Effects in S_N1 and S_N2

The effect of a solvent on a reaction can be complex and difficult to predict. In the laboratory there is a large amount of trial and error associated with choosing a solvent. In the classroom solvents are normally grouped into three broad categories listed below from *least* polar to *most* polar:

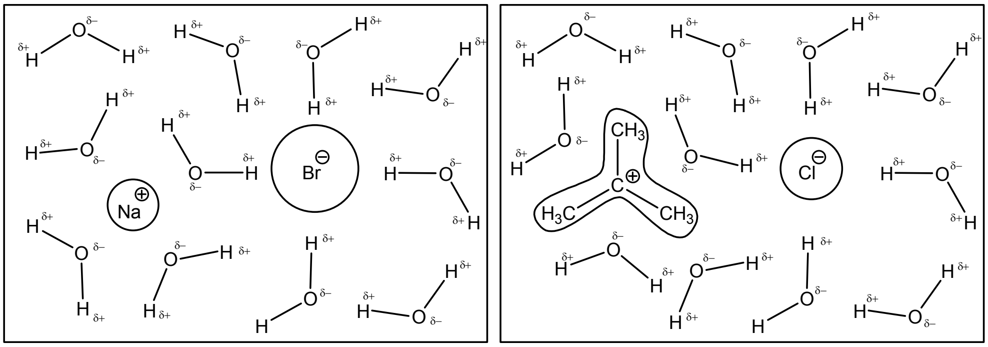
(least polar) **nonpolar solvents** (e.g., pentane, cyclohexane, benzene, decane, CCl_4, etc.)

polar aprotic solvents = polar solvents without an H on N, O or X

(most polar) **polar protic solvents** = polar solvents with an H on N, O or X

In general, like dissolves like. Since substitutions always involve polarized molecules and partial or full charges (e.g. carbocations), nonpolar solvents do not dissolve such reactants and are not used for S_N1/S_N2.

The large δ+ and δ– charges of a polar protic solvent allow it to make H-bonds to negative ions and H-bond like interactions to positive ions. This lowers the potential energy of either kind of ion.



NaBr dissolved in water
(NaBr is a reagent used for delivering the nuclephile bromide ion)

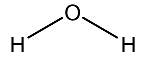
***t*-butyl chloride dissociated in water**
(t-butyl chloride pictured *after* chloride has left)

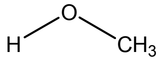
Figure 13.5: Cartoons of water (an example of a polar protic solvent) stabilizing both + and – ions

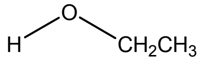
Critical Thinking Questions

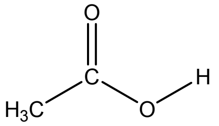
56. Use dotted lines to mark H-bonds and other [⊖ -to-δ+] or [⊕ -to-δ–] interactions in Figure 13.5.

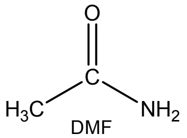
57. Label each common solvent as nonpolar (NP), polar aprotic (PA), or polar protic (PP).

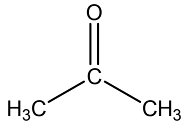

water

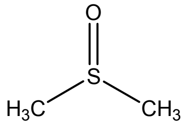

methanol

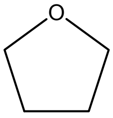

ethanol

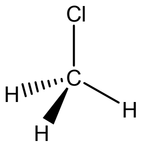

acetic acid

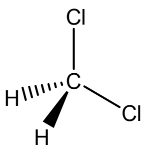

DMF

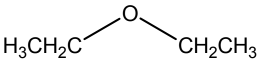

acetone

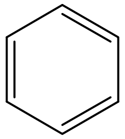

DMSO

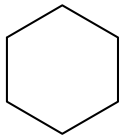

THF

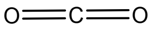

chloroform

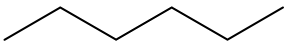

dichloromethane

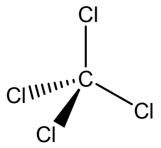

diethyl ether


benzene

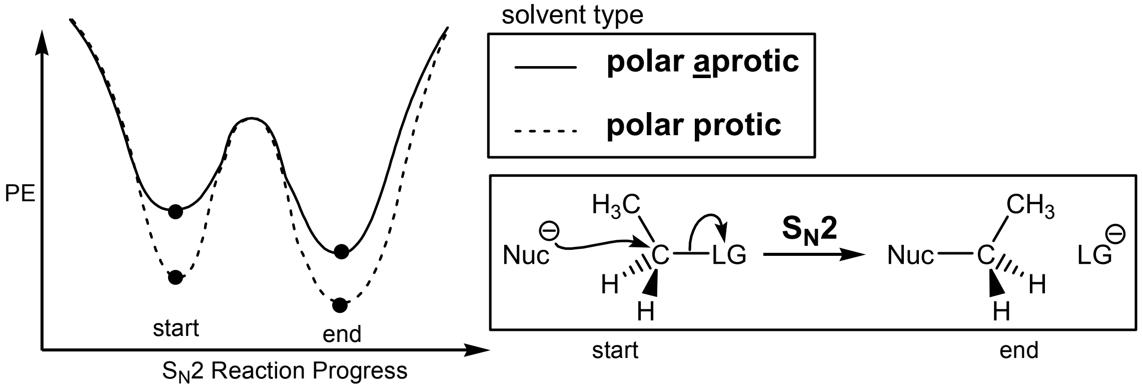

cyclohexane


liquid carbon dioxide


hexane


carbon tetrachloride

58. Shown below are reaction profiles for an S_N2 reaction in a polar aprotic solvent (solid line) vs. a polar protic solvent (dotted line).



a. For each reaction pathway, draw a vertical arrow representing the activation energy (E_{act}).

b. In which solvent is E_{act} smaller for S_N2, **polar aprotic** or **polar protic**? (circle one)

c. Based on information in Model 10, explain why a polar protic solvent lowers the PE of the nucleophile in an S_N2 reaction. *(It also lowers the PE of the LG, but this has little impact on the rate.)*

d. What is the effect of lowering the PE of the nucleophile on the rate of S_N2 reaction?

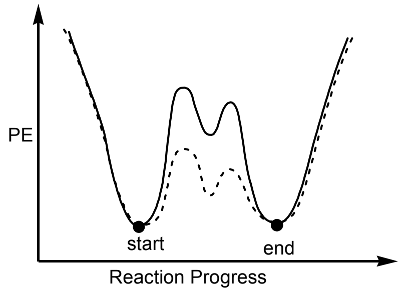
e. Which is faster, an S_N2 in a **polar aprotic** or **polar protic** (circle one) solvent?

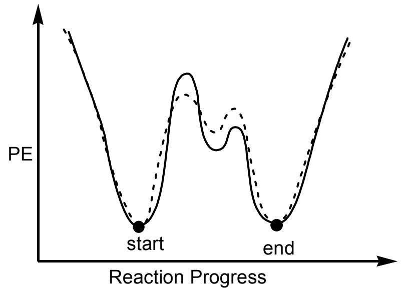
Memorization Task 13.8: One useful statement of the Hammond postulate

In the 1950s Iowa State University chemist George S. Hammond postulated that, for two similar reactions, the one with the lower-energy intermediate will also have a lower-energy transition state (and thus a faster rate). This rule of thumb is one useful statement of the **Hammond postulate**.

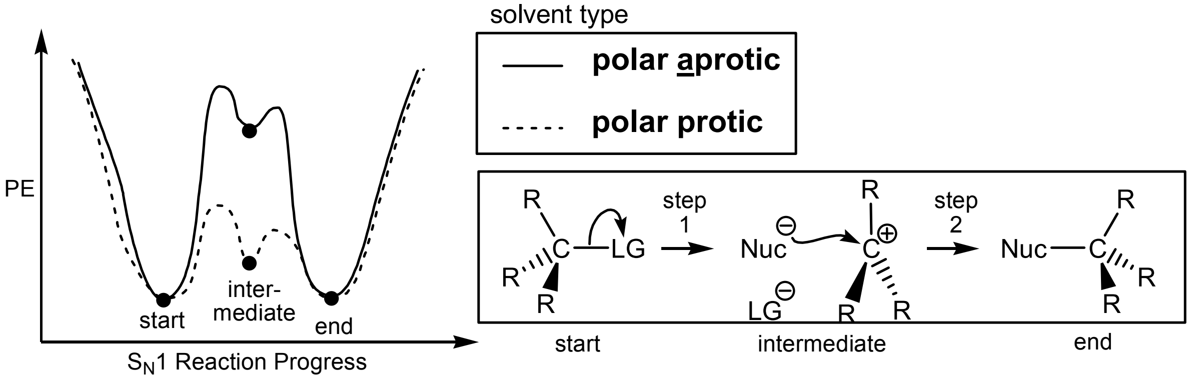
Critical Thinking Questions

59. On which energy diagram do the two reaction profiles (solid line and dotted line) obey the rule of thumb in Mem. Task 13.8? On which energy diagram do they violate this rule of thumb?





60. Shown below are energy diagrams for an **S_N1** reaction in a polar aprotic solvent (solid line) vs. a polar protic solvent (dotted line).



a. For each reaction pathway, draw a vertical arrow representing the activation energy (E_{act}).

b. In which solvent is E_{act} smaller for S_N1, **polar aprotic** or **polar protic**? (circle one)

c. Based on information in Model 10, explain why a polar protic solvent lowers the PE of the intermediate in an S_N1 reaction.

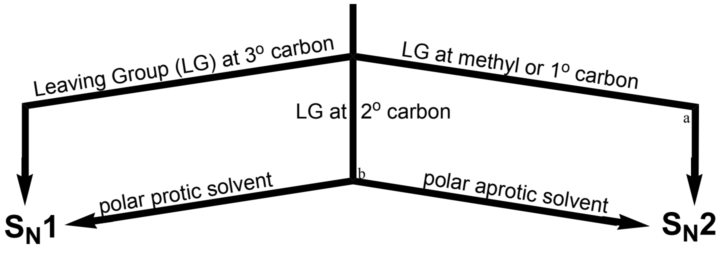
d. What is the effect of lowering the PE of the carbocation on the rate of an S_N1 reaction? (Assume the Hammond postulate holds for this reaction.)

e. Which is faster, an S_N1 in a **polar aprotic** or **polar protic** (circle one) solvent? How does this answer compare to your answer for an S_N2 reaction (*See* part e on the previous page.)?

Memorization Task 13.9: Polar protic solvents impede (slow) S_N2, and speed S_N1.
(Check your work.) Is this consistent with your answers to CTQ 58 and CTQ 60?

Model 11: S_N1 vs. S_N2

You should be able to explain each branch point on this decision tree, but while you work toward this goal it may help to memorize parts of it.

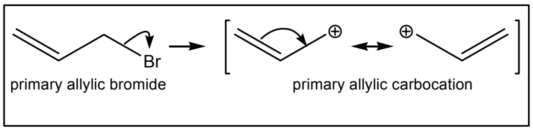


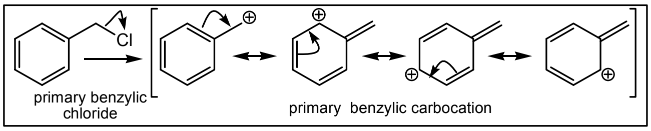
Critical Thinking Questions

61. (Review) For each of the following, briefly explain why the statement is true, and then identify the branch or branches of the decision tree in Model 11 that go with the statement.
    a. S_N2 reactions do NOT take place at 3° electrophilic carbons.
    b. S_N1 reactions do NOT take place at methyl or 1° electrophilic carbons.
    c. A substitution reaction at a 2° carbon can go by either an S_N1 or an S_N2 mechanism depending largely on a key variable. (What is this variable?)

Model 12: What about allylic and benzylic electrophilic carbons?

Recall that **allylic carbocations** and **benzylic carbocations** are very favorable due to resonance stabilization and therefore are very likely to form as intermediates during a reaction.

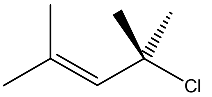


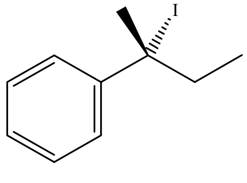


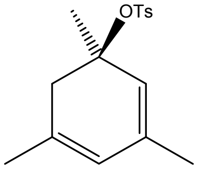
Critical Thinking Questions

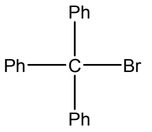
62. Ordinary primary alkyl halides cannot undergo S_N1. However, in a polar protic solvent the alkyl halides in Model 12 *can* undergo S_N1. What is special about these that allows them to do this?

63. Like many allylic and benzylic alkyl halides, the examples in Model 12 can undergo either S_N1 or S_N2 (depending on the solvent). However, this is not always the case. Explain why the following allylic and benzylic alkyl halides CANNOT undergo an S_N2 regardless of solvent.

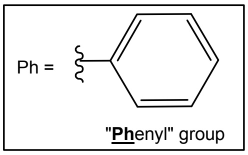








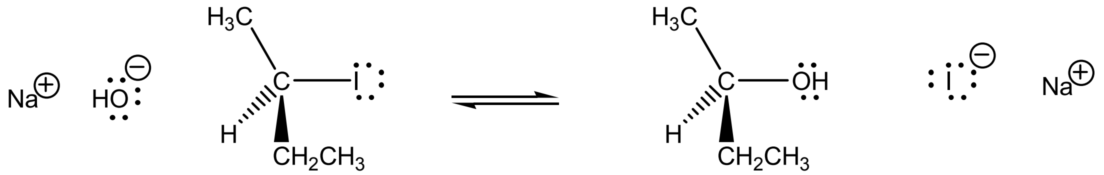
$\mathrm{Ph_3C{-}Br}$



64. Find the small "a" and "b" on the decision tree in Model 11. Draw a line between these points. Label this pathway "**LG on allylic or benzylic carbon,**" and explain why this new branch is needed.

Exercises for Part A

1. Determine the absolute configuration of each chiral molecule below.



   a. Explain why the reaction above would NOT produce the organic product shown in a one-step nucleophilic substitution reaction.

   b. Draw the *correct* product of an S_N2 reaction for the reactants above.

2. The product shown above, (R)-2-butanol, can be made via reaction of (S)-2-iodobutane and NaOH.

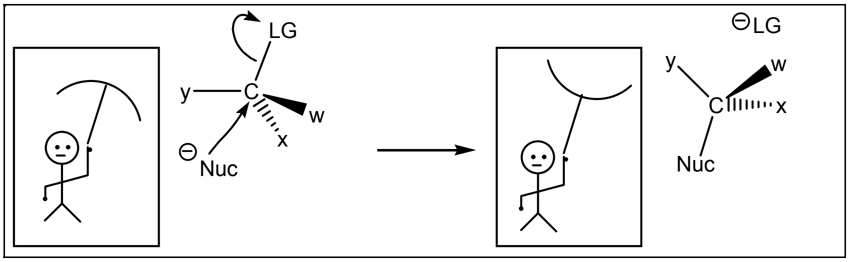
   a. Use curved arrows to show this reaction.

   b. Draw an energy diagram for this reaction. Include on your energy diagram wedge-and-dash drawings of the reactants, transition state, and products. In your transition-state drawing, use a dotted line to indicate a partial bond and δ– to indicate partial negative charge on an atom.

   c. Write the rate expression for this reaction.

3. Explain why a one-step nucleophilic substitution reaction is called an S_N2 reaction.

4. One-step nucleophilic substitution reactions at a chiral carbon are characterized by the inversion of the absolute configuration of this carbon. Your model set is not very useful for simulating this **chiral inversion**. Explain how the model set falls short and how an umbrella in the wind can sort of simulate this inversion.



5. Show the mechanism and products of an S_N2 reaction between water and methyl iodide.

6. Read the assigned pages in the text, and do the assigned problems.

Exercises for Part B

7. Draw the full structure of each reactant and reagent; then draw the products of each reaction.

$$CH_3CH_2CH_2Cl \xrightarrow{NaSCH_3}$$

$$CH_3CH_2CH_2Cl \xrightarrow{KCN}$$

$$CH_3CH_2CH_2Cl \xrightarrow[\text{Ph= phenyl group } (C_6H_5)]{PPh_3}$$

$$CH_3CH_2CH_2OTs \xrightarrow{KOH}$$

$$\text{(R)-2-bromobutane} \xrightarrow{KOH}$$

$$CH_3CH_2CH_2Br \xrightarrow{NaC{\equiv}CCH_2CH_3}$$

$$CH_3CH_2CH_2OTs \xrightarrow{NaI}$$

$$\text{(R)-2-bromobutane} \xrightarrow{CH_3OH}$$

$$CH_3OH \xrightarrow[\textit{better accomplished using } SOCl_2]{HCl}$$

$$\text{3-pentanol} \xrightarrow[\textit{better accomplished using } PBr_3]{HBr}$$

$$\text{(S)-2-iodopentane} \xrightarrow{NaN_3}$$

$$CH_3OH \xrightarrow{H_2SO_4 \qquad H_2S}$$

$$CH_3I \xrightarrow{CH_3CO_2Na}$$

$$CH_3I \xrightarrow[\substack{\textit{a special reagent called LDA} \\ \textit{Lithium DiisopropylAmide}}]{((CH_3)_2CH)_2N^{\ominus} \quad Li^{\oplus}}$$

$$CH_3I \xrightarrow{NaOCH_2CH_3}$$

$$CH_3CH_2OSO_2CH_3 \xrightarrow{H_2O}$$

$$CH_3OSO_2CF_3 \xrightarrow{NaOCH_2CH_3}$$

$$CH_3CH_2CH_2OSO_2tol \xrightarrow{NaBr}$$

$$CH_3I \xrightarrow{NaNH_2}$$

$$HCCH \xrightarrow{NaNH_2} \quad \xrightarrow{CH_3I}$$

8. Consider a reaction between NaOH and 2-iodopropane and a reaction between NaOH and 2-chloropropane.
   a. Draw the reactants.
   b. Add curved arrows to show a one-step nucleophilic substitution reaction.
   c. Draw the most likely products of each reaction.
   d. Predict, based on the data in Table 13.1, which reaction will be faster.
   e. Draw an energy diagram showing both reactions on the same set of axes. Draw the 2-iodopropane reaction profile with a dotted line and the 2-chloropropane reaction profile with a solid line, and assume that the potential energies of the reactants and the potential energies of the products are the same in both reactions (i.e., the only difference is in the energies of the two different transition states).

9. Fill each blank with one of the following words (some may be used twice, some not at all). **weak, strong, low, high**, **up, down**, **large, small, good, poor, soft,** or **hard**.

Leaving groups tend to follow p*K*$_a$ trends, so, since a good leaving group is generally a _______ base, the conjugate acid of a good leaving group will have a _________ pK_a.)

The opposite generally is true for nucleophiles (_________ base = good nucleophile), but there are some exceptions. Notably halogens are __________ bases but unexpectedly __________ nucleophiles.

In each column of the periodic table, nucleophilicity increases as you go _________. This means that HS^- and I^- are very ________ nucleophiles.

A partial explanation for this trend is that atoms in rows three, four and five of the periodic table have ________ fluffy orbitals. Such nucleophiles are called __________ nucleophiles or bases. (Counterexample: A nucleophile like F^- has ________ orbitals and is therefore called a ________ nucleophile or base.)

_________ nucleophiles are malleable and tend to make lower-energy transition states and thus fast substitution-reaction rates.

10. Circle each species on Table 13.2 below that is an unexpectedly good nucleophile based on the pK_a's of their conjugate acids.

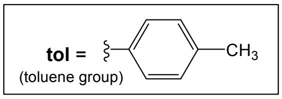
R = H or alkyl

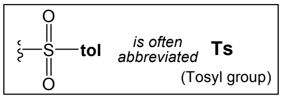
Very Good Leaving Groups	**Good Leaving Groups**	**Poor Leaving Groups**
RSO_3^- *(most often… R= CF_3, R= tol, or R= CH_3)* I^-	R_2O *(water, alcohol, or ether)* Br^- Cl^-	F^- *strong bases are very poor leaving groups* RO^- R_2N^- R_3C^-

Table 13.1: Common Leaving Groups

Very Good Nucleophiles	**Good Nucleophiles**	**Poor Nucleophiles**
RS^- NC^- I^- PR_3 $*R_3C^-$ $*R_2N^-$ $*RC{\equiv}C^-$ $*RO^-$	Br^- R_2S NR_3 Cl^- RCO_2^- N_3^-	F^- HCO_3^- R_2O *(water, alcohol, or ether)* *All strong acids are very poor nucleophiles*

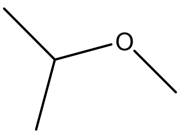
Table 13.2: Common Nucleophiles

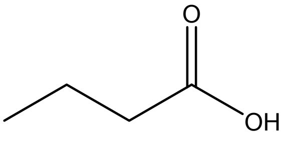


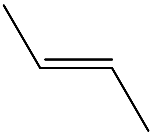


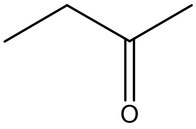
**These nucleophiles are also strong bases. They will NOT undergo S_N2 reactions when there is a faster acid-base pathway available (more on this later).*

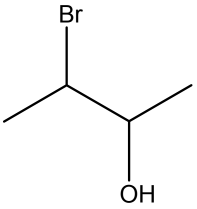
11. Show a synthesis of each target starting from a primary or methyl alkyl halide and any reagents containing three or fewer carbons.





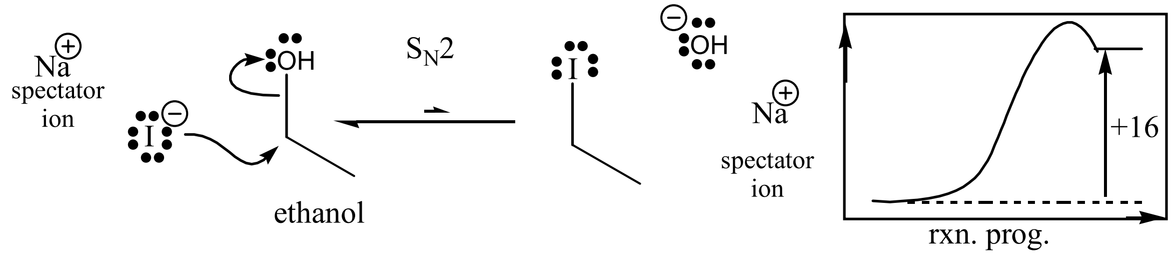






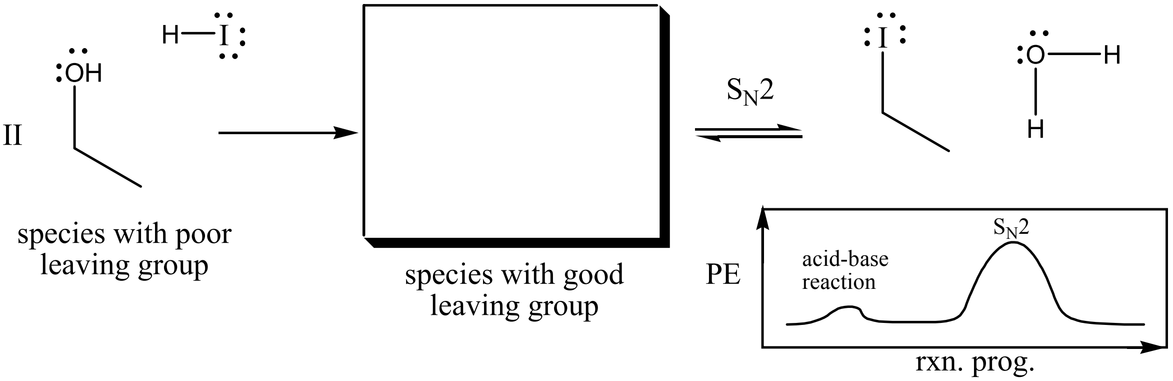
12. Construct an explanation for why this reaction between ethanol and NaI is uphill (not favorable).

I.



13. Show the two-step mechanism of the reaction between ethanol and HI.

II


H—I
OH
species with poor leaving group
species with good leaving group
SN2
I
O—H
H
PE
acid-base reaction
SN2
rxn. prog.

a. Construct an explanation for why this reaction is much more favorable (see energy diagram) than the reaction with NaI.

b. Explain why water (OH_2) is a better leaving group than hydroxide (HO^-).

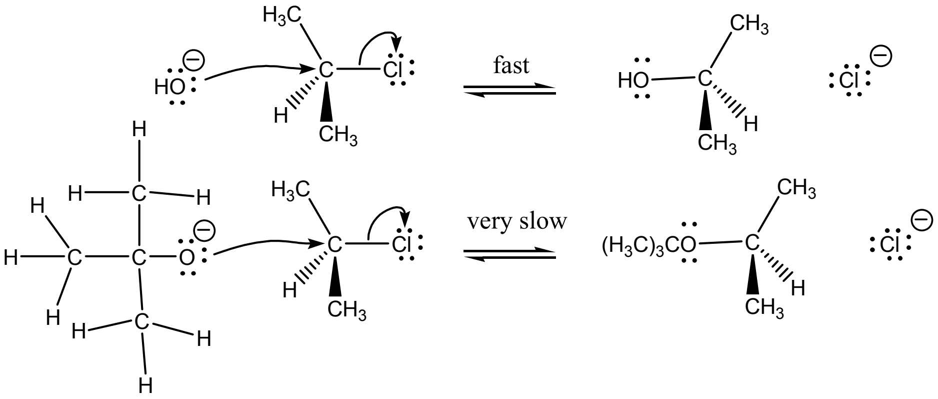
c. HCl can replace HI in the reaction above to produce an alkyl chloride, but there is a better reagent to convert a primary or secondary alcohol to an alkyl chloride. What is this reagent?

d. HBr can replace HI in the reaction above to produce an alkyl bromide, but there is a better reagent to convert a primary or secondary alcohol to an alkyl bromide. What is this reagent?

14. Read the assigned pages in the text, and do the assigned problems.

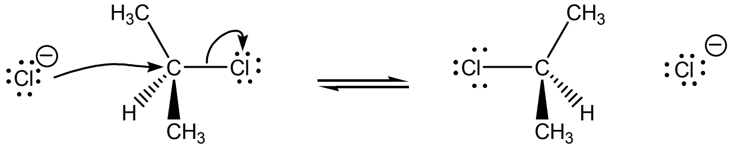
Exercises for Part C

15. In general a strong base (high P.E.) is a good nucleophile. Construct an explanation for the following exception. Both nucleophiles shown (hydroxide and *tert*-butoxide) are strong bases, but only one of them is good nucleophile.



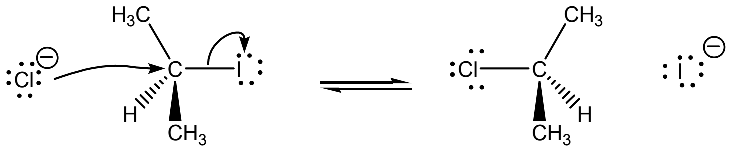
16. Consider the following reactions.
    a. Construct an explanation for why Rxn A is slower than Rxn B.
    b. Construct an explanation for why Rxn A is slower than Rxn C.
    c. Construct an explanation for why Rxn A is slower than Rxn D.

A.



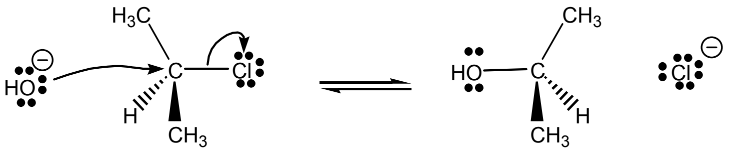
Rel. Rate = 1

B.



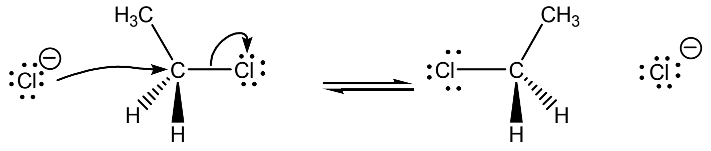
Rel. Rate = 1000

C.



Rel. Rate = 10

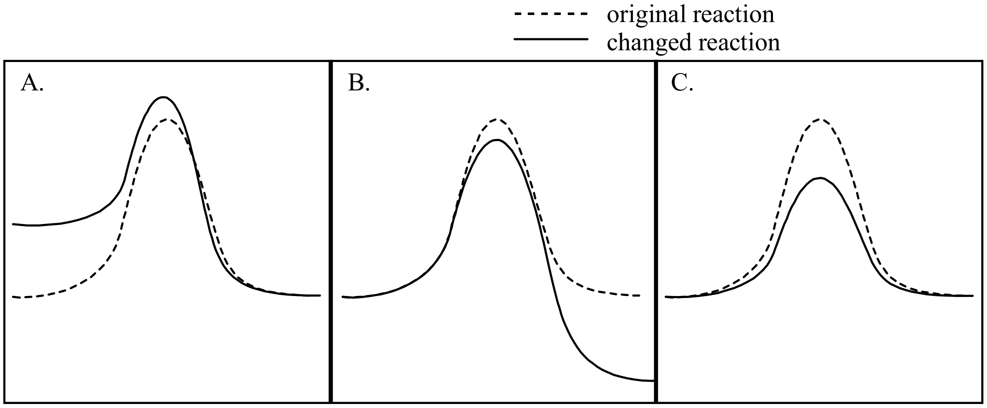
D.



Rel. Rate = 100

17. Use curved arrows to show an S_N1 and S_N2 pathway for Reaction V in Model 7.
    a. Draw an energy diagram with both reaction profiles.
    b. Write a rate expression for both reaction pathways.
    c. Explain why the S_N2 pathway is so much slower.

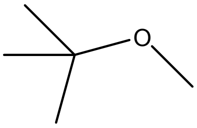
18. Each energy diagram below shows two reaction profiles. The dotted line shows the original reaction, and the solid line shows the reaction after a change has been made. Match each of the following changes with the correct energy diagram below.
    (1) Change to a better nucleophile.
    (2) Change from a secondary electrophilic carbon to a primary electrophilic carbon.
    (3) Change to a better leaving group.

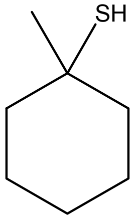


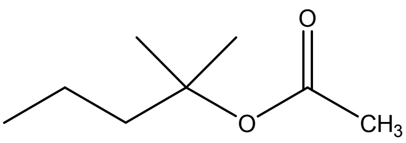
19. Give an example of a pair of reagents that are more likely to undergo S_N1 than S_N2, and vice versa.

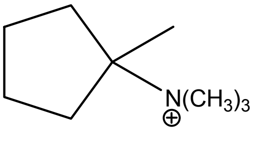
20. The products formed in Reaction VII in Model 7 are not a racemic mixture. What term best describes the relationship between the two chiral products shown, and why is this not a racemic mixture?

21. Show a synthesis of each target starting from a tertiary alkyl halide and any reagents containing three or fewer carbons.









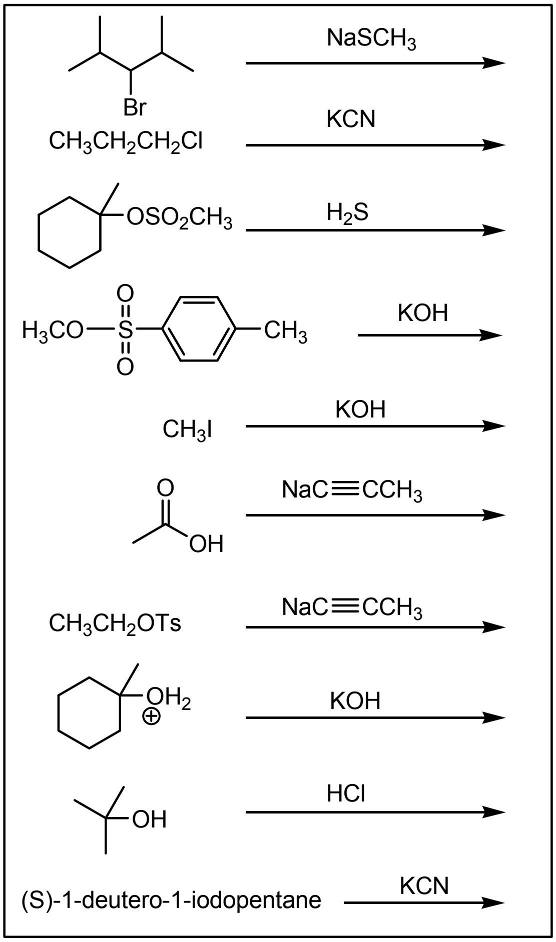
22. Read the assigned pages in the text, and do the assigned problems.

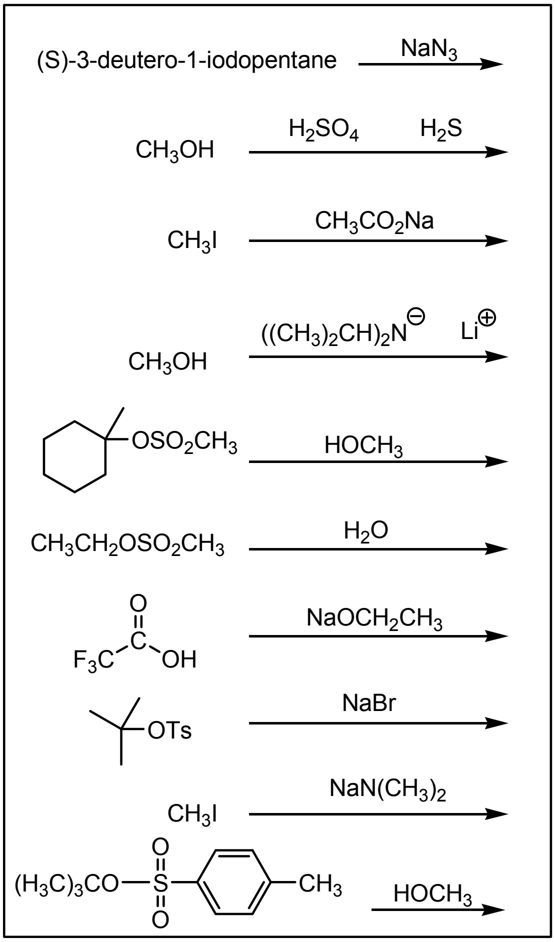
Exercises for Part D

23. Explain why a polar protic solvent speeds the rate of an S_N1 mechanism.

24. Explain why a polar protic solvent slows the rate of an S_N2 mechanism.

25. For each reaction, draw the most likely product, and indicate which of the following is most likely: [S_N1], [S_N2], [acid-base (H^+ transfer) with no substitution reaction], [acid-base followed by S_N1], [acid-base followed by S_N2], or [S_N1 with carbocation rearrangement likely].





26. In CTQ 60, the polar protic solvent lowers the potential energy of the nucleophile (along with the carbocation). In doing so, the solvent deactivates the nucleophile, yet this does not slow the rate of the reaction. Explain.

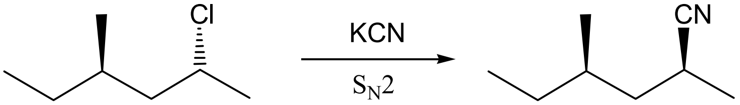
27. Read the assigned pages in the text, and do the assigned problems.

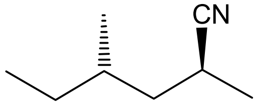
The Big Picture

As you will see in the next activity, substitution is not the only reaction that can occur when a nucleophile is mixed with a molecule containing a good leaving group. There is a whole other family of reactions called elimination reactions. We will focus on two of them whose names are E1 and E2. Things get quite complex in ChemActivity 14, so do yourself a favor, and make sure you are very comfortable with the concepts here in ChemActivity 13, including knowing the mechanisms of S_N1 and S_N2 and why a given pair would go by one mechanism versus the other.

Common Points of Confusion

- S_N2 reactions are one-step while S_N1 reactions are two-step. (It's as if we are *trying* to confuse and frustrate you!) The "1" and "2" in S_N1 and S_N2 DO NOT refer to the number of steps in the reaction. They refer to the number of species involved in the slowest step of each reaction.
- Chiral inversion in an S_N2 reaction ONLY occurs at the electrophilic carbon because it is caused by the nucleophile making a new bond and the leaving group leaving. This will be clear if you go through the mechanism of the reaction. Unfortunately, students sometimes cut corners and simply memorize that S_N2 causes **chiral inversion**. When faced with a reaction such as the one below, such students incorrectly assume that the result of the reaction is to invert ALL chiral centers.





This is not the S_N2 product, as some students assume.

- A simple analysis of the difference between S_N1 and S_N2 will lead, at this point, to the correct conclusion that S_N1 is favored when there is a tertiary (allylic or benzylic) leaving group, and S_N2 is favored when there is a primary (or methyl) leaving group. It is fine to memorize this distinction at this point, but be aware that for the next set of reactions (called E1 and E2) this distinction does not hold up. Specifically, E2 reactions, though they are similar to S_N2 reactions in some ways, can occur when there is a primary ***or*** tertiary leaving group (or any other type of leaving group). This trips up many students and is explained in greater detail in the Common Points of Confusion section of the next ChemActivity.

ChemActivity 14: Elimination

PART A: TWO-STEP ELIMINATION (E1)

(By what mechanism does a molecule that can form a favorable carbocation become an alkene?)

Model 1: *p* Orbital to *p* Orbital Conjugation

Neighboring *p* orbitals that are parallel to one another can interact to form a bond-like attraction. This attraction (called **conjugation**) is favorable and lowers the overall potential energy of the molecule.

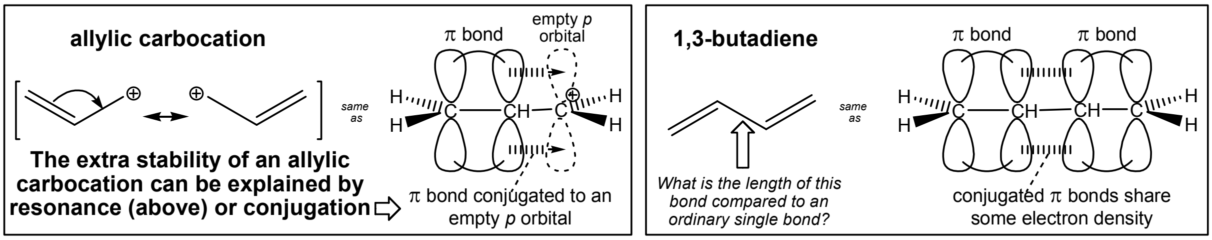

allylic carbocation
same as
π bond
empty p orbital
H
C
CH
The extra stability of an allylic carbocation can be explained by resonance (above) or conjugation
π bond conjugated to an empty p orbital
1,3-butadiene
same as
What is the length of this bond compared to an ordinary single bond?
π bond
π bond
conjugated π bonds share some electron density

Figure 14.1: Examples of conjugation in an allylic carbocation and 1,3-butadiene

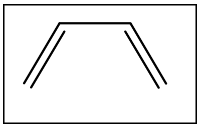
Critical Thinking Questions

1. Construct an explanation for why the bond marked with an arrow on **1,3-butadiene** in Figure 14.1 is found experimentally to be slightly shorter than a typical single bond.

2. As you cool a diene such as 1,3-butadiene, rotation of the single bond between the two π bonds (marked with arrow on Figure 14.1) stops long before rotation of an ordinary single bond.

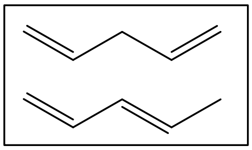
   a. Construct an explanation for why such a bond behaves this way.

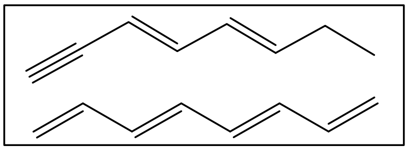
   b. At low temperature two different conformations of 1,3-butadiene can be isolated and identified. The conformation shown in Figure 14.1 is called **s-*trans***-1,3-butadiene. Construct a name for this other conformation → →

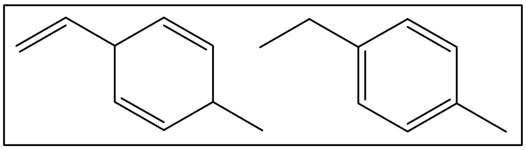


   c. Given that the "**s**" stands for "**s**ingle" bond, explain the names "**s-cis**" and "**s-trans**".

3. For each pair of constitutional isomers, circle the one that is lower in potential energy.

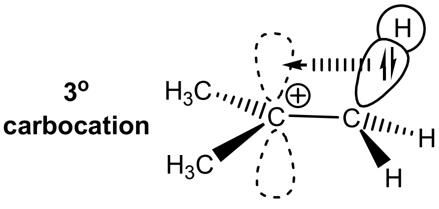




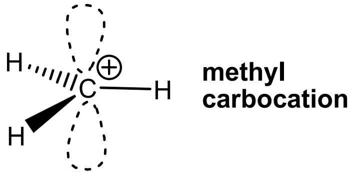


Model 2: *p* Orbital to σ Bond (weak) Conjugation = "Hyperconjugation"

Rotation of the C—C bonds on the carbocation below allows each of the nine equivalent C—H σ bonds to briefly align with the empty *p* orbital and donate electron density to it. This stabilizes the carbocation.



each C-H σ bond can donate electron density as it rotates past and briefly aligns with the empty *p* orbital



Because the *p* orbital and σ bond are not perfectly parallel, this effect, called **hyperconjugation**, is weaker than the proper conjugation between two parallel *p* orbitals (as shown in Model 1).

Hyperconjugation is the primary argument for why 3° carbocations are comparatively very favorable.

Critical Thinking Questions

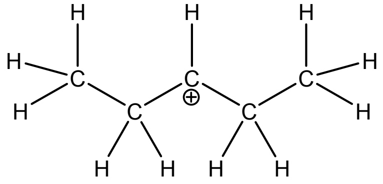
4. Explain why the methyl carbocation in Model 2 is much less favorable than the 3° carbocation.

5. Construct an explanation for why a C–H σ bond on the 3° carbocation in Model 2 is momentarily weakened while it is aligned with the neighboring empty *p* orbital.

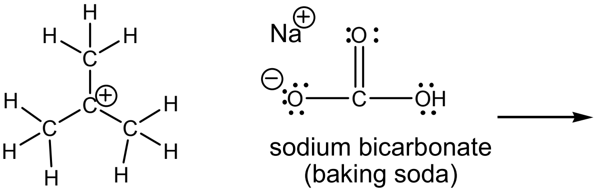
6. It turns out that this effect is powerful enough to lower the pK_a of most carbocations to zero.

   a. (Review) A pK_a of zero means it is **easy** or **difficult** (circle one) to pull an H off a carbocation.

   b. All nine H's on the carbocation in Model 2 are equivalent, so any one could be associated with the pK_a of zero. This is not the case for the carbocation at right → Only four of these H's are easy to pull off. Circle these four H's, and explain your reasoning.



7. A tertiary carbocation is such a strong acid it will react with even a very weak base.



sodium bicarbonate
(baking soda)
weak base & poor nucleophile

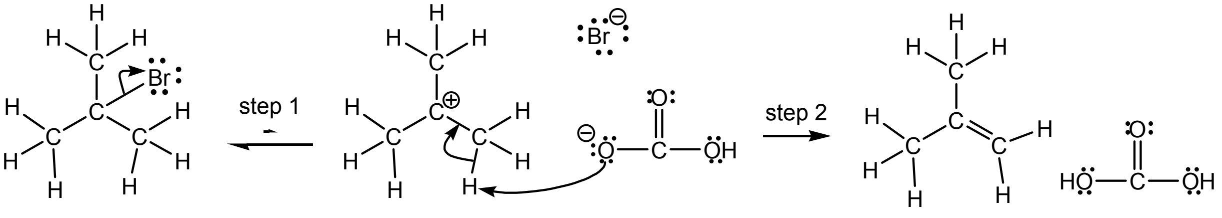
   a. Use curved arrows to show the mechanism and the products of this acid-base reaction.

   b. It is possible to draw the organic product of this reaction with all zero formal charges. Have you drawn this most important representation of the C_4H_8 product? If not, draw it.

Model 3: Two-Step Elimination (E1)

In the absence of a good nucleophile, a molecule that can form a favorable carbocation will lose its leaving group and an H to form an alkene. (Often the solvent is a strong enough base to pull off the H.)

This "elimination" of a LG and H to form a double bond is called a **two-step elimination (or E1)**.



Critical Thinking Questions

8. (E) Identify the **leaving group** (LG) and **H** that are "eliminated" in the reaction above.

9. (Review) In Model 3 it says this reaction works only in the absence of a good nucleophile. What different reaction mechanism would be likely if a good nucleophile (such as I^-) were present above?

10. Consider the following rate data for the two-step elimination in Model 3.

[R—Br]	$[HCO_3^-]$ (baking soda)	Relative Rate
1 M	1 M	1
2 M	1 M	2
1 M	2 M	1

Table 14.1: Rate dependence on concentration for Two-Step Elimination

a. Is the reaction rate dependent on the concentration of R—Br? … base (baking soda)?

b. Write a rate expression for this two-step elimination.

c. A **two-step elimination** is usually called an "**E1**" reaction. Explain both the "E" and the "1," and why this is an appropriate name for this reaction.

d. Draw an energy diagram for the E1 above. (*Hint*: Which is the slowest/rate-limiting step?)

Term Introduction: α, β, γ, δ, etc. Carbons and Hydrogens

Chemists use the Greek letters α, β, γ, δ, etc., to designate how far away a particular carbon atom is from a carbocation or group other than C or H (e.g., a leaving group such as Cl or Br). *For example*,

- the "**alpha-carbon**" (C_α) is the carbocation carbon or the C attached to the leaving group,
- the "**beta-carbon**" (C_β) is one carbon away from the leaving group/carbocation carbon,
- the "gamma-carbon" (C_γ) is two carbons away from the leaving group/carbocation, etc.,

A hydrogen attached to a C_α is called an "alpha-hydrogen" (H_α); an H on a C_β is called H_β, etc.

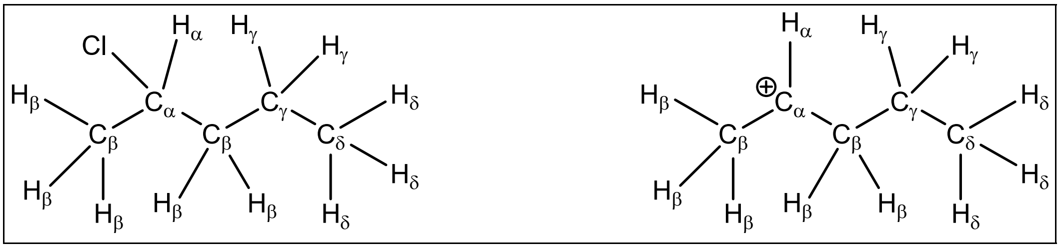
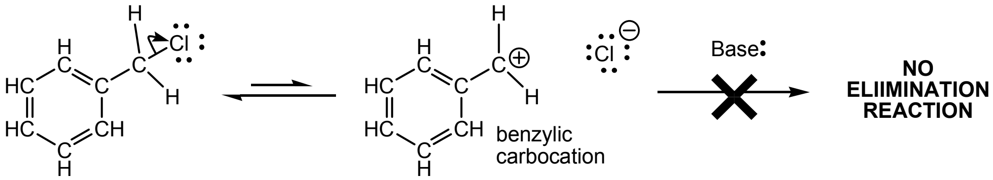


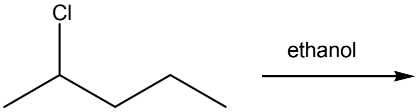
Figure 14.2: Naming system for C's and H's relative to the position of a functional group

Critical Thinking Questions

11. Explain why the following molecule CANNOT undergo elimination even though it readily forms the very favorable benzylic carbocation shown.



12. Circle each H on the alkyl chloride in Figure 14.2 that is susceptible to being eliminated by a weak base when the leaving group (Cl) leaves, and the carbocation shown above right is formed.
    a. What one type of H (which Greek letter) can be eliminated in an E1 reaction?
    b. (Check your work.) Is your answer to the previous question consistent with the fact that this type of elimination reaction is sometimes called a **beta-elimination**?
    c. Draw the three alkene products that can be produced by elimination of Cl and an H_β from the following alkyl chloride. (*Hint*: Two products are *E/Z* isomers of each other.)



Model 4: Mono-, Di-, Tri-, and Tetra-substituted Alkenes

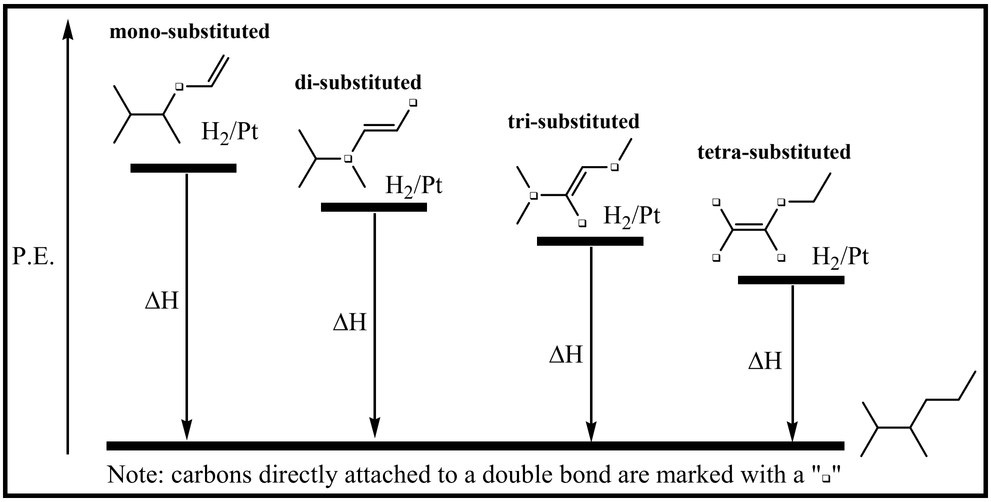


Figure 14.3: Catalytic hydrogenation of Various C_8H_{16} constitutional isomers

Critical Thinking Question

13. (E) How many C's are directly attached to the two C's of the double bond in a **mono-substituted** alkene? …**di-substituted** alkene? …**tri-substituted** alkene? …**tetra-substituted** alkene?

Memorization Task 14.1: Alkene Potential Energy

The more substituted an alkene → the lower its potential energy (see Figure 14.3).

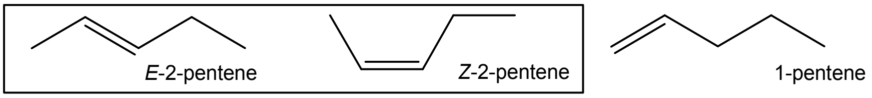
Memorization Task 14.2: Zaitsev's Rule

In an elimination the most substituted (lower PE) alkene product will dominate the product mixture.

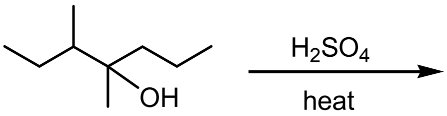
Critical Thinking Questions

14. (Check your work.) All three structures below are produced by the E1 reaction at the bottom of the previous page, but only the two in the box are observed in significant quantities. Does this reaction obey **Zaitsev's rule**? Explain your reasoning.

(Note: E dominates slightly over Z because of steric factors; the alkyl groups are more spread out in E.)



15. A common type of E1 involves heating an alcohol in acid. Draw all five possible alkene products of this reaction, circle the two you expect to dominate the product mixture, and cross out the one you expect will be least abundant. *Check your work: See Exercise 1 AFTER you complete the question.*



PART B: ONE-STEP ELIMINATION (E2)

(Why will an S_N2 reaction often fail with a nucleophile that is also a strong base?)

Model 5: "Patient" and "Impatient" Bases

A weak base (such as bicarbonate) is too weak to pull an H from an electrophile until the leaving group has left. In the words of the patient/impatient analogy, a weak base must wait patiently for a carbocation to form. Note: Carbocation formation takes a long time relative to most other types of reactions.

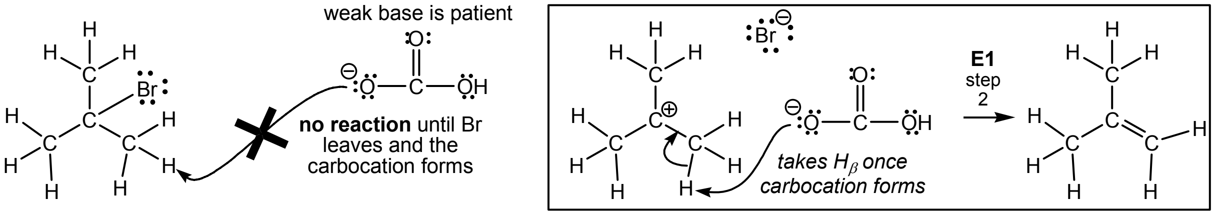

weak base is patient
no reaction until Br leaves and the carbocation forms
E1
step
2
takes Hβ once carbocation forms

Figure 14.4: Weak base must wait patiently for a carbocation to form

In contrast a strong base can rip an H_β off an electrophile without waiting for the leaving group to leave. In the words of the analogy, a strong base is impatient and does not wait for a carbocation to form. By taking this H_β, the **strong base** initiates a **one-step elimination (E2)** reaction.

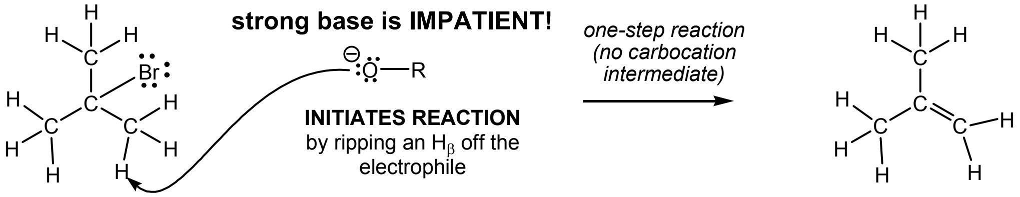

strong base is IMPATIENT!
INITIATES REACTION
by ripping an Hβ off the electrophile
one-step reaction
(no carbocation intermediate)

Figure 14.5: Strong base initiates a reaction by taking a beta hydrogen

Critical Thinking Questions

16. (Review) What is our definition of a strong base? (*See* Memorization Task 4.1)

17. Add two curved arrows to Figure 14.5 to complete the one-step elimination with a strong base.

18. Consider the following rate data for the reaction in Figure 14.5.

[R—X]	RO^- (base)	Relative. Rate
1 M	1 M	1
2 M	1 M	2
1 M	2 M	2
2 M	2 M	4

Table 14.2: Rate data for one-step elimination

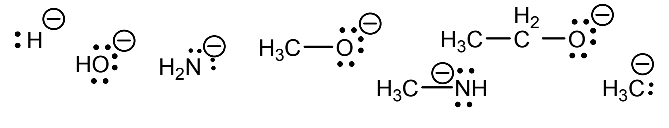
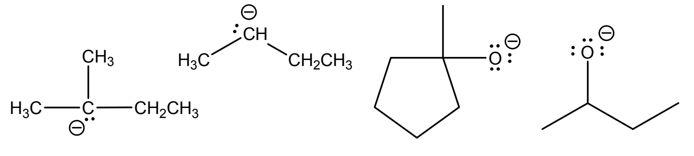
a. Is the rate dependent on the concentration of R—X? … base (RO^-)?

b. Write a rate expression for this reaction.

c. A **one-step elimination** is usually called an "**E2**" reaction. Explain both the "E" and the "2," and why this is an appropriate name for this reaction.

Model 6: E2 Reactions—Strong Bases (definition of small vs. large)

Different product ratios are often achieved when using a small vs. a large base in an E2 reaction. We will use definitions (below) of small and large similar to those we used for nucleophiles in CA 13.

Small Base single atom, methyl, or primary, but not next to a branch point	
Large Base tertiary, secondary, or primary next to a branch point (attached directly to a 2° or 3° atom)	

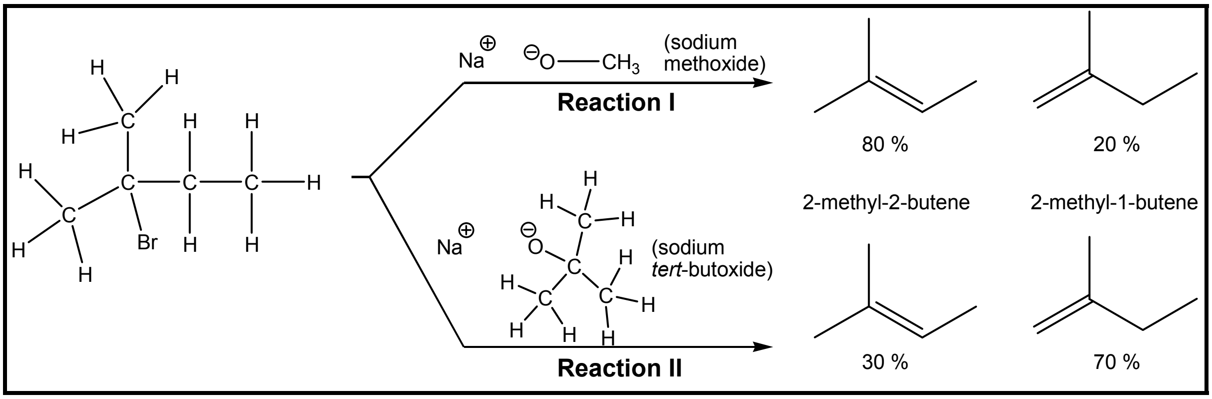


Figure 14.6: Effect of base size on product ratios for E2 reactions

Critical Thinking Questions

19. Label each of the two bases in Figure 14.6 as being small or large.

20. Which is lower in potential energy: **2-methyl-2-butene** or **2-methyl-1-butene** (circle one)?

21. For Reaction I and Reaction II, determine if each follows Zaitsev's rule. *(See Memorization Task 14.2.)*

22. Put a box around each H_β on the starting alkyl bromide that could be removed to produce the tri-substituted product (2-methyl-2-butene).

23. Circle each H_β on the starting alkyl bromide that could be removed to produce the di-substituted product (2-methyl-1-butene).

24. A small base (such as methoxide) is small enough to get at any H_β on the starting material.
    a. Use curved arrows to show the mechanism of Reaction I leading to the major product shown.
    b. Explain why methoxide preferentially removes a boxed H_β.

    c. Use curved arrows to show the mechanism of Reaction II leading to the major product shown.
    d. Construct an explanation for why it is easier for *tert*-butoxide to remove a circled H_β than a boxed H_β.

Term Introduction: Zaitsev Product vs. Hofmann Product

Zaitsev product = most-substituted alkene product of an elimination reaction (*follows* **Zaitsev's rule**)

Hofmann product = least-substituted alkene product of an elimination reaction (*violates* **Zaitsev's rule**)

The Hofmann product is named for 19th-century German chemist August Wilhelm von Hofmann, who developed an elimination using a $N(CH_3)_3$ *leaving group that also violates the rule named for his Russian contemporary, Alexander Mikhaylovich Zaitsev.*

Critical Thinking Questions

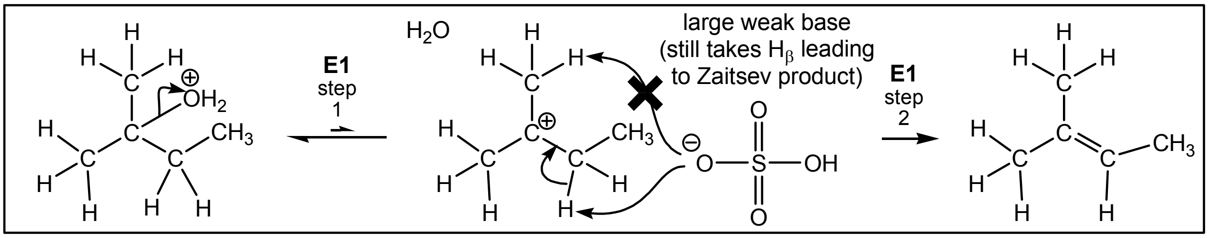
25. Label the Zaitsev and Hofmann products in Figure 14.6.
26. Draw the structure of a base that would give an even higher percentage of the Zaitsev product than methoxide in Reaction I.

Memorization Task 14.3: Only E2 reactions with a small base obey Zaitsev's Rule.

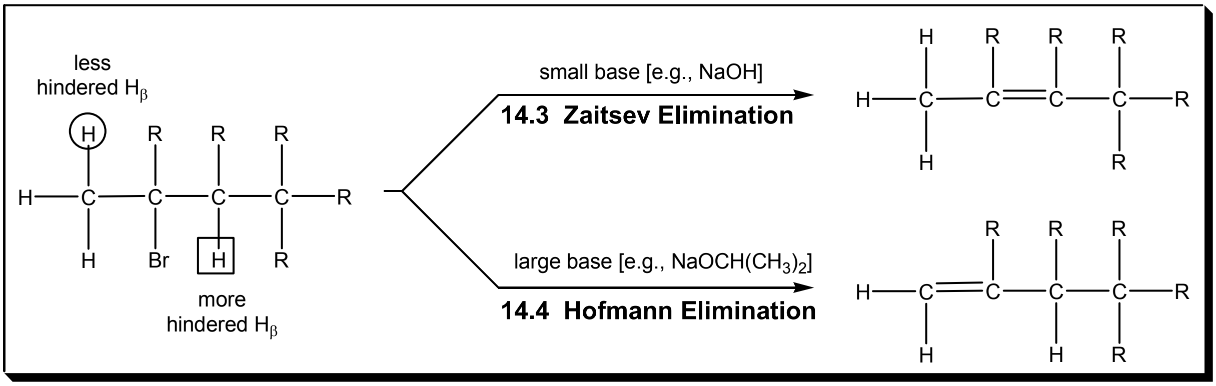
A small base can get to any H_β, so it selectively removes the H_β leading to the lowest PE alkene. Due to steric repulsion, a large base is forced to pull off the least-hindered H_β, leading to the Hofmann product.

Memorization Task 14.4: E1 reactions always obey Zaitsev's Rule (E1—Zaitsev)

This is a common point of confusion because many weak bases (e.g., the conjugate base of sulfuric acid) are quite large. Regardless of size, a weak base will always favor taking the H_β that leads to the lowest-potential-energy alkene (the most substituted alkene).



Synthetic Transformations 14.3 and 14.4: E2—Zaitsev or Hofmann



Model 7: E2 in Competition with S_N2

Any small, strong base is also a good nucleophile, which opens the possibility of S_N2 competing with E2. Under ordinary conditions, the following reactant pairs give a mixture of S_N2 and E2 products.

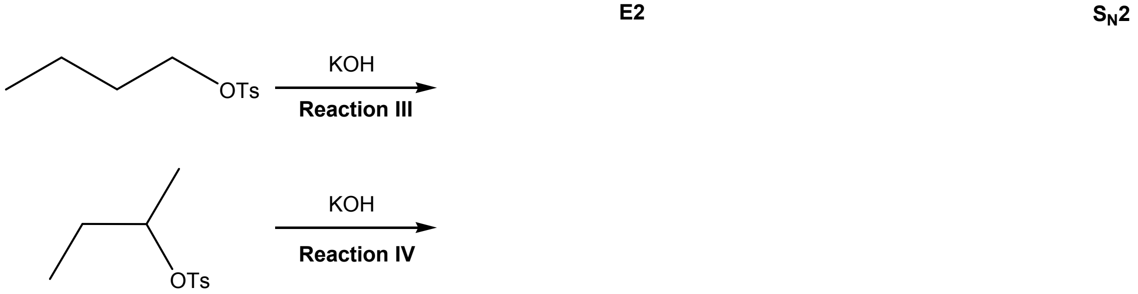


Figure 14.7: Reactants that simultaneously undergo competing E2 and S_N2 reactions

Memorization Task 14.5: Heat favors elimination (over substitution)

For reasons we will not discuss here, higher reaction temperatures favor elimination over substitution.

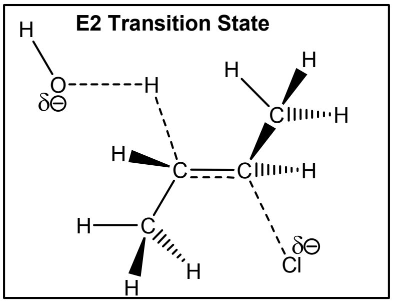
Critical Thinking Question

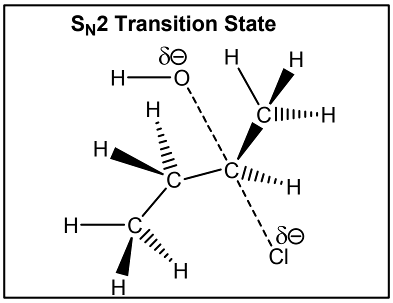
27. Draw the major E2 product **and** the major S_N2 product for ***each*** reaction in Figure 14.7.
28. In which reaction in Figure 14.7 is S_N2 more likely to dominate over E2? Explain your reasoning.

29. According to Model 7, how can a mixed-mechanism reaction be pushed toward S_N2 or E2?

30. Is your answer to the previous question consistent with the fact that Reaction IV in Figure 14.7 gives an alkene as the major product at 80°C and an alcohol as the major product at 10°C?

31. Drawn at right are the E2 and S_N2 transition states ($ts^{\ddagger}$) for Reaction IV in Figure 14.7.



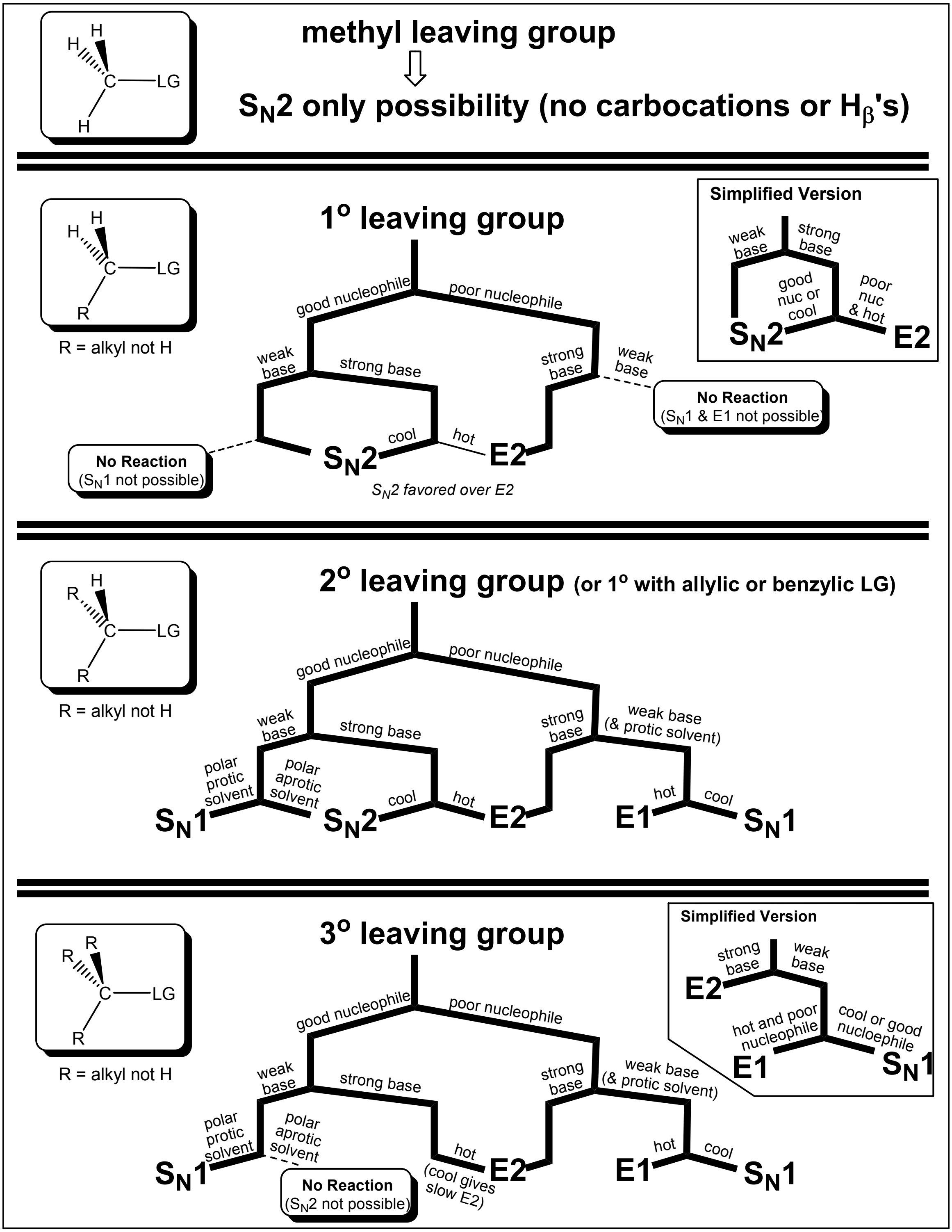


   a. In which $ts^{\ddagger}$ does HO^{-} experience more steric hindrance while making the new bond? Explain your reasoning.

   b. Construct an explanation for why increasing the size of the base/nucleophile in a mixed E2/S_N2 reaction will increase the amount of E2 product relative to S_N2 product. (e.g., replacing the H of OH with an alkyl group).

Memorization Task 14.6: S_N1, S_N2, E1, E2 (Decision Tree)

Don't try to memorize this by brute force*. Start by answering the CTQ's on the next page with your group or study partner. Only then should you try to draw the trees from memory without looking at the original.*



Use this diagram to answer the CTQ's on the following page.

Critical Thinking Questions

32. Construct an explanation for each of the following generalizations:
    a. S_N1 and E1 are not possible with 1° leaving groups (unless allylic or benzylic).
    b. S_N2 is not possible with 3° leaving groups.
    c. Strong base favors E2 when a beta hydrogen is present.
    d. Polar-protic solvents favor S_N1 and E1.
    e. Methyl alkyl halides can only do S_N2.
    f. A larger nucleophile/base favors elimination over substitution.

33. For a strong base/good nucleophile and a 2° leaving group, what variable can push the reaction toward S_N2 vs. E2?

34. For a weak base/good nucleophile and a secondary alkyl halide, what variable can push the reaction to S_N2 vs. S_N1?

35. Give specific reagents/conditions that fit the following criteria: 2° alkyl halide and…
    a. strong base that would undergo S_N2
    b. weak base that would undergo S_N2
    c. good nucleophile that would undergo E2
    d. poor nucleophile that would undergo E2
    e. reagents that would undergo E1
    f. reagents that would undergo S_N1

MAKE MODELS: BROMOCYCLOHEXANE & (S)-2-BROMOBUTANE

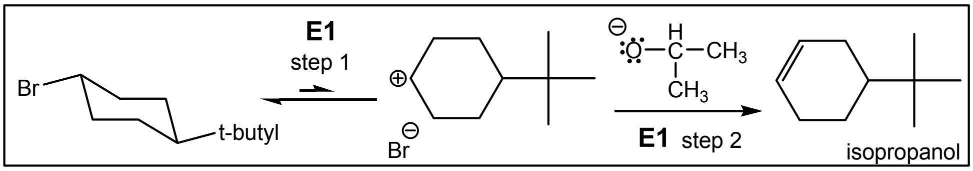
PART C: STEREOCHEMISTRY OF E2 REACTIONS

(Why can't Reaction VII, below, do E2?)

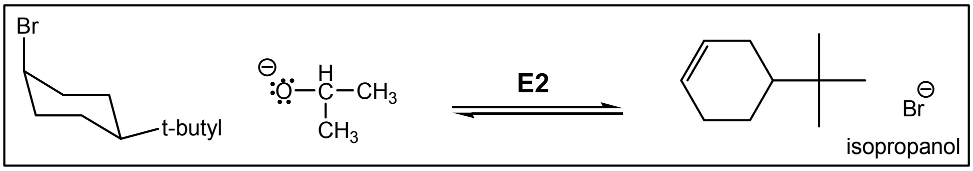
Model 8: Leaving Group Position in an E2 Reaction

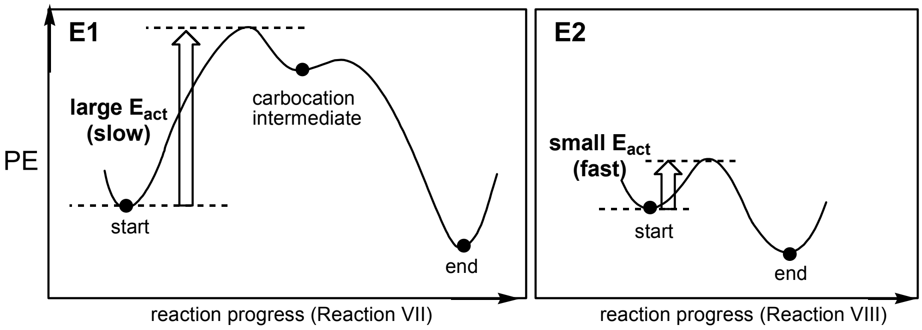
Reaction VII is a **very rare** example of an E1 reaction that takes place in the presence of a strong base. In this activity we will learn why Reaction VII cannot do E2 despite the fact that a strong base favors E2).

Reaction VII



Reaction VIII





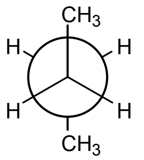
Critical Thinking Questions

36. Label one of the 1-bromo-4-*t*-butylcyclohexane configurational stereoisomers in Model 8 *trans* and the other *cis*. (It may help to draw in the H's on C_1 and C_4 of the ring.)

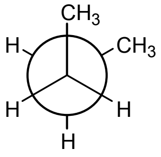
    a. For each configurational stereoisomer, label the leaving group (Br) as axial or equatorial. (Recall that a t-butyl group is "locked" in the more roomy equatorial position.)

    b. Complete the statement using only evidence from Model 8: E2 is possible on a substituted cyclohexane ring ONLY when the LG is in an **axial** or **equatorial** (circle one) position.

Memorization Task 14.7: Review of Newman Projection Terminology



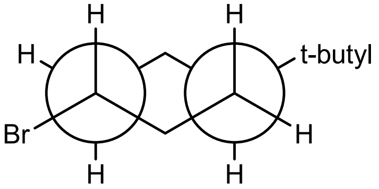
the two methyl groups are said to be **anti to one another**



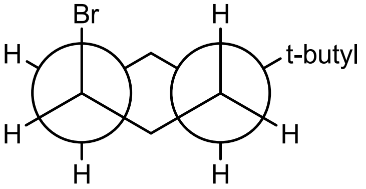
the two methyl groups are said to be **gauche to one another**

Model 9: Newman Projections of Molecules from Model 8

Assume t-butyl is locked in an equatorial position. This means a **ring flip** is impossible, and each 1-bromo-4-*tert*-butylcyclohexane molecule is locked in the conformation shown.



trans-1-bromo-4-*tert*-butylcyclohexane



cis-1-bromo-4-*tert*-butylcyclohexane

Make a model of 1-bromo-4-*t*-butylcyclohexane (represent Br and *t*-butyl with different color balls).

Critical Thinking Questions

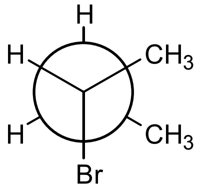
37. Circle each H_β shown as an "H" on the Newman projections in Model 9.
(Note: Each structure also has two other H_β's that are not shown as "H" due to the rules of skeletal structures.)

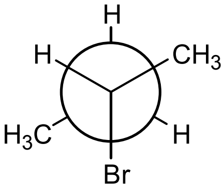
38. Based on the information on the previous page, write the words "**E2 favorable**" under one structure in Model 9 and "**E2 impossible-must go by E1**" under the other, and explain your reasoning.

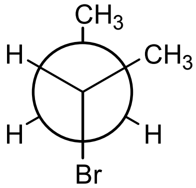
39. Circle the one statement that is consistent with your conclusions above.

- For an E2 reaction to occur there must be an H_β **gauche** to the leaving group.
- For an E2 reaction to occur there must be an H_β **anti** to the leaving group.

40. Make a model of (S)-2-bromobutane, and confirm that all possible staggered conformations sighting down the C_2-C_3 bond are shown below.







a. Based on your conclusion in the previous question, cross out the conformation that **cannot** lead to an E2 reaction.

b. Which of the remaining two conformations is more favorable in terms of potential energy? Explain your reasoning.

41. Below are Newman and "sawhorse" representations of the two conformations of (S)-2-bromobutane that can lead to E2 reactions, along with the products of these E2 reactions.

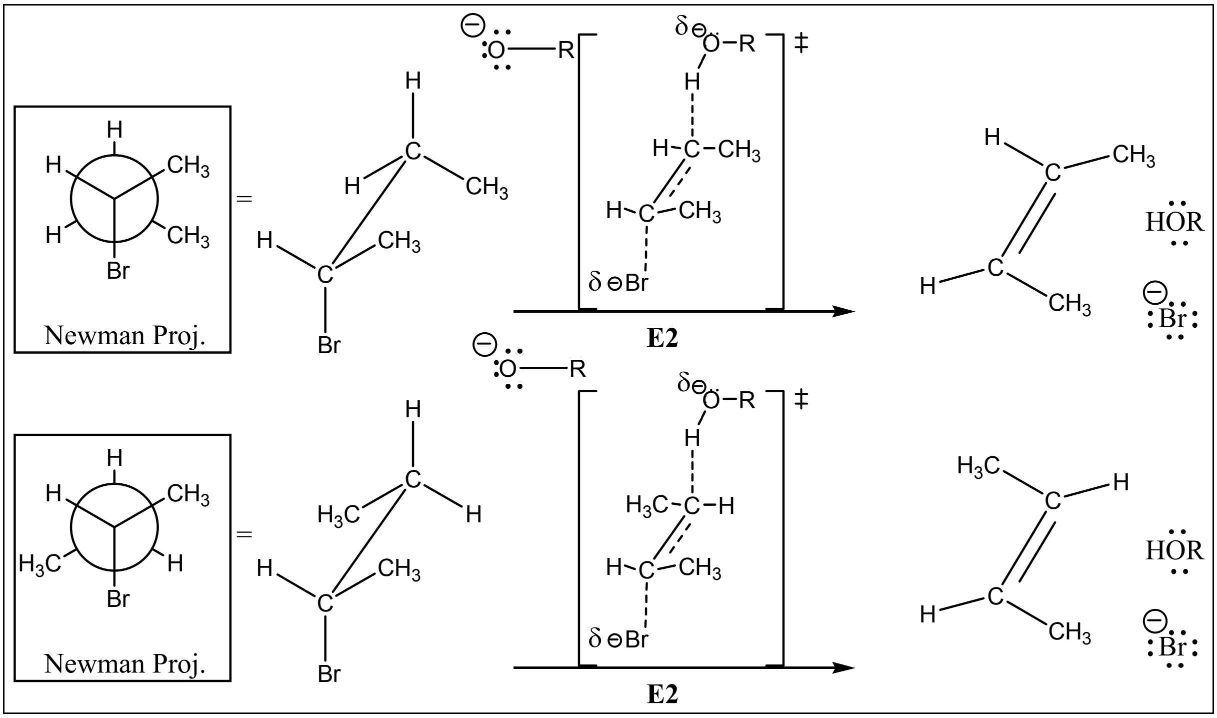


Figure 14.8: Conformations and transition states leading to *Z*- and *E*-2-butene

a. On the sawhorse representations of the reactants above, use curved arrows to show the flow of electrons during each E2 reaction. *(S_N2 may also occur depending on temperature and R group.)*

b. (Check your work.) Are your curved arrows consistent with the electron changes depicted in the transitions state for each reaction?

c. Label one of the products *Z*-2-butene and the other *E*-2-butene.

42. Fill the blanks in the following paragraph with "***gauche,***" "***anti,***" "***E,***" or "***Z,***" as appropriate.

The reactions above are E2 reactions, so the changes happen all at once in one step. This means that…

If the base takes the H when the methyl groups are ____________ to one another, this "**traps**" the methyl groups **on the same side** of the newly forming double bond and leads to the ____ product.

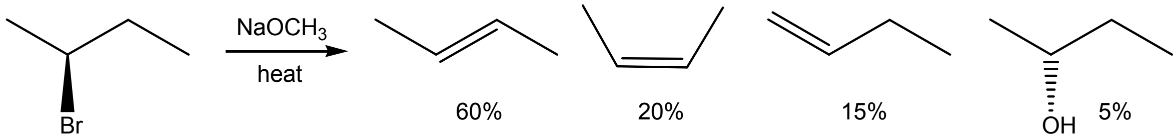
In contrast…

If the base takes the H when the methyl groups are ____________ to one another, this "**traps**" the methyl groups **on opposite sides** of the newly forming double bond and leads to the ____ product.

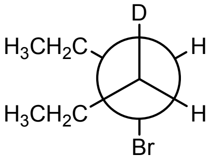
43. Label one of the Newman projections above with the words "**lower P.E.—will spend more time in this conformation.**"

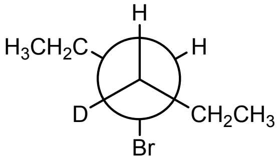
44. Predict which will be more prevalent in the product mixture: ***E*-2-butene** or ***Z*-2-butene** (circle one), and explain your reasoning.

45. (Check your work.) Is your answer to the previous CTQ consistent with this product distribution?



46. Consider two conformations of one configurational stereoisomer of 3-bromo-4-deuterohexane shown below using Newman projections. Though, in practice, D is harder to remove than H (this is called an **isotope effect**), assume for this question that D has identical reactivity to H in an E2.

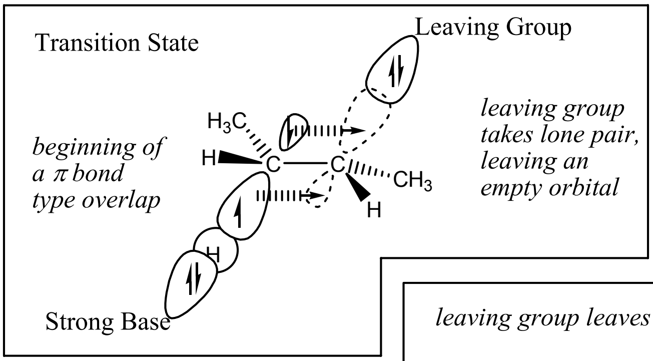


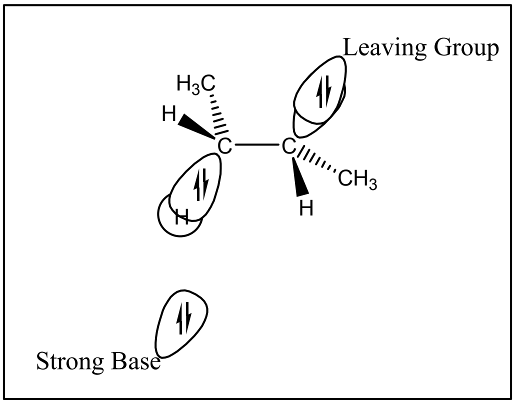


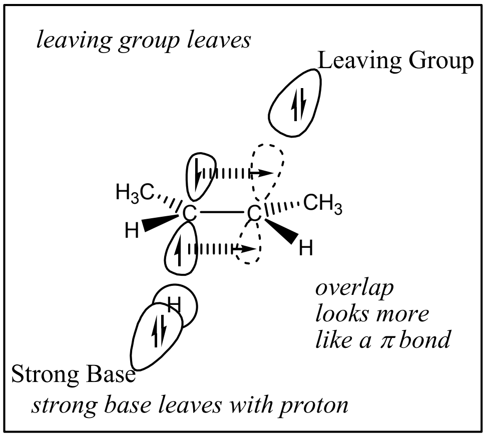
a. Next to each, draw the product that will form if the conformation shown undergoes E2.

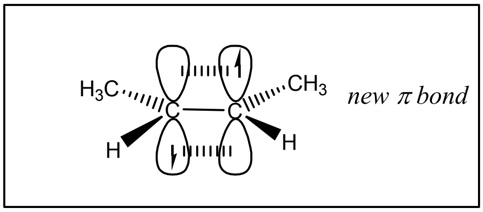
b. Circle the product you expect to dominate the product mixture, and explain your reasoning.

47. Label the boxes at right with 1, 2, 3, 4 to show the order in which they occur in an E2 reaction.


Transition State
Leaving Group
beginning of a π bond type overlap
leaving group takes lone pair, leaving an empty orbital
H3C
H
C
C
CH3
H
H
Strong Base

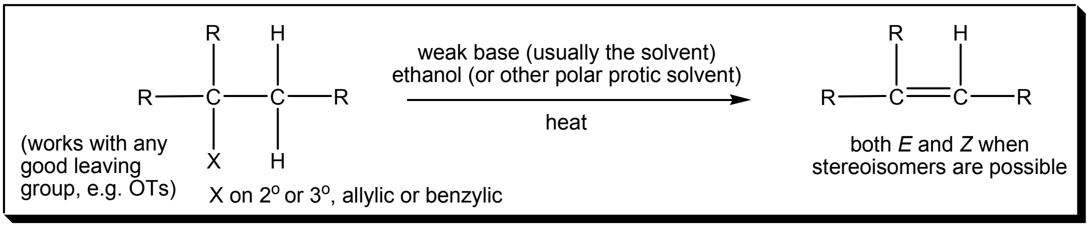



leaving group leaves
Leaving Group
H3C
C
C
CH3
H
H
overlap looks more like a π bond
H
Strong Base
strong base leaves with proton

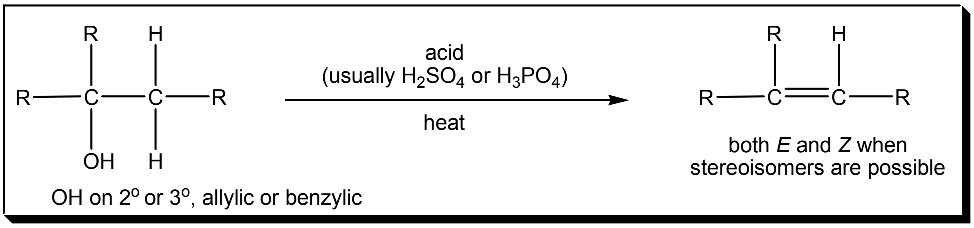


Exercises for Part A

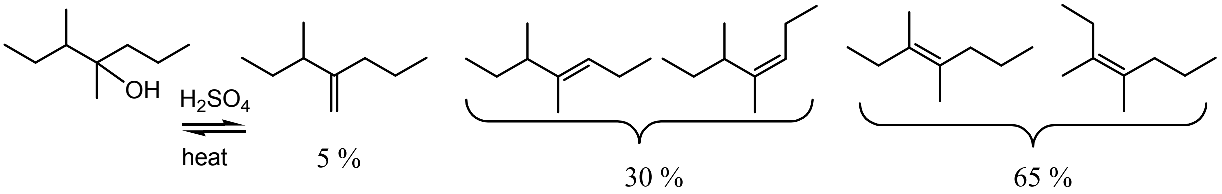
Synthetic Transformation 14.1: Alkyl Halide (R—X) or Tosylate (R—OTs) to Alkene (via E1)


weak base (usually the solvent)
ethanol (or other polar protic solvent)
heat
(works with any good leaving group, e.g. OTs)
X on 2° or 3°, allylic or benzylic
both *E* and *Z* when stereoisomers are possible

Synthetic Transformation 14.2: 2° or 3°, allylic or benzylic Alcohol to Alkene (via E1)


acid
(usually H_2SO_4 or H_3PO_4)
heat
OH on 2° or 3°, allylic or benzylic
both *E* and *Z* when stereoisomers are possible

1. (Check your work.) Are the following product ratios consistent with your answer to CTQ 15?



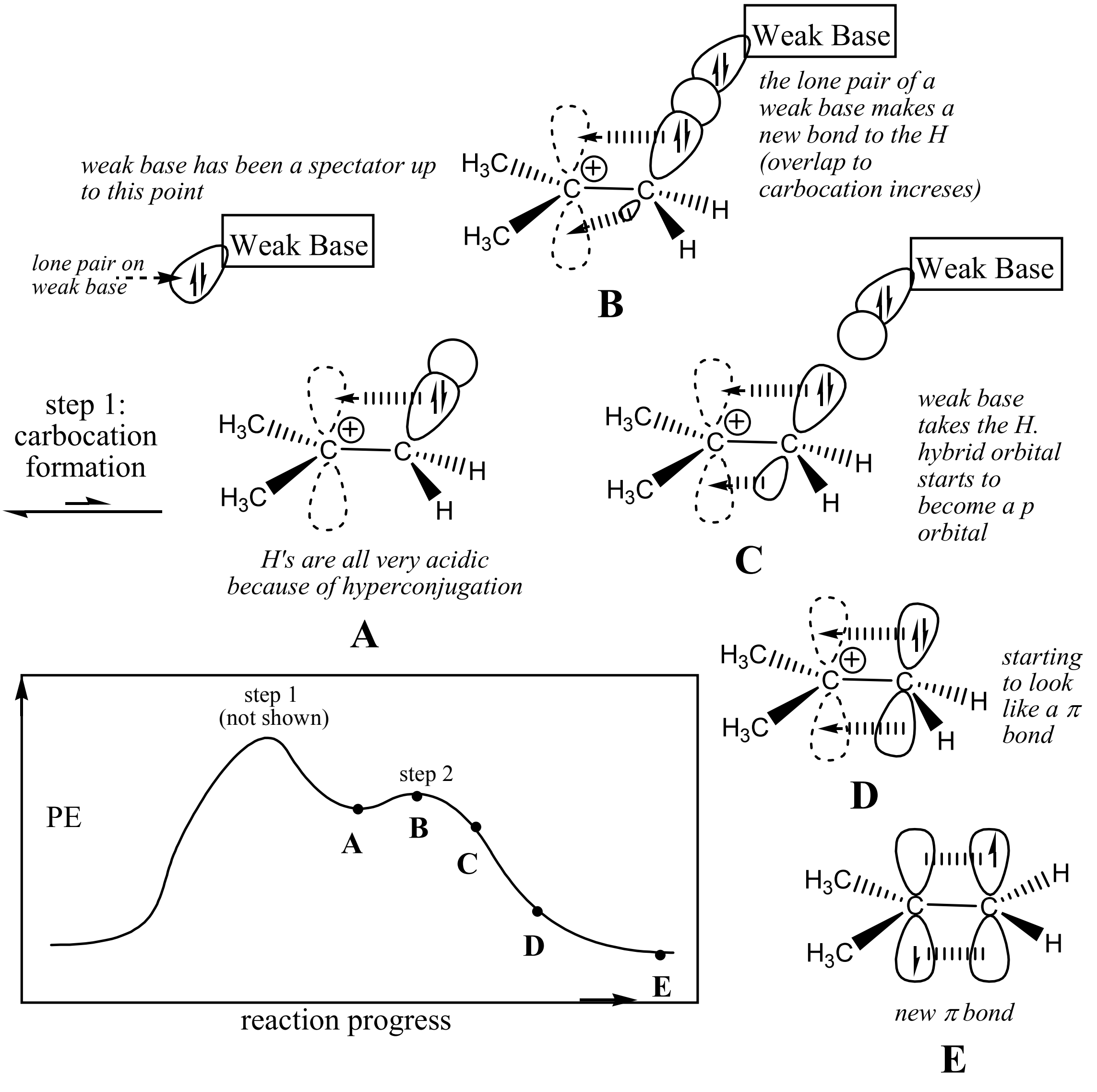
   a. Label each alkene product with a word describing the level of substitution of the double bond.
   b. Label each double bond among the products as *E, Z,* or neither.
   c. Use curved arrows to show the mechanism of formation of the disubstituted product and a representative tri- and tetra-substituted product.

2. Show the mechanism of Synthetic Transformation 14.1.
   a. Draw an energy diagram showing this reaction.
   b. Write a rate expression for this reaction.

3. Show the mechanism of Synthetic Transformation 14.2, and draw an energy diagram (assume the acid-base reaction is much faster than either step in the elimination).

4. A good nucleophile (bromide) *is* present in the reaction in Model 3. Does Br^- react with the carbocation, and if so, what product is formed when it does?

5. Which point (of A-E) is the transition state of step 2 of an E1 reaction? Draw this transition state using dotted lines to represent partial bonds and δ's to represent partial charges.

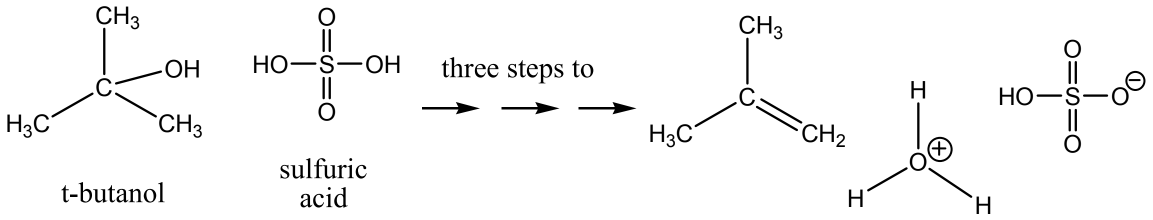

Weak Base
the lone pair of a weak base makes a new bond to the H (overlap to carbocation increses)
weak base has been a spectator up to this point
H_3C
C
⊕
C
H
H_3C
H
Weak Base
lone pair on weak base
B
Weak Base
step 1: carbocation formation
H_3C
C
⊕
C
H
H_3C
H
weak base takes the H. hybrid orbital starts to become a p orbital
H's are all very acidic because of hyperconjugation
C
A
starting to look like a π bond
step 1 (not shown)
step 2
PE
A
B
C
D
E
reaction progress
D
new π bond
E

6. One carbon involved in the reaction above changes hybridization state during the reaction. Label this carbon with its hybridization state in A (start) and in E (end).

7. An **un-substituted** alkene has a molecular formula of C_2H_4. Draw the structure of this molecule and explain why it is called **unsubstituted**. (This is the only "unsubstituted" alkene.)

8. According to the information in Figure 14.3, what is the relationship between the level of substitution of a double bond and the potential energy of the alkene?

9. The result of mixing *t*-butyl alcohol and sulfuric acid is shown below. Use curved arrows to show the entire mechanism of this reaction, and draw the two intermediate products.

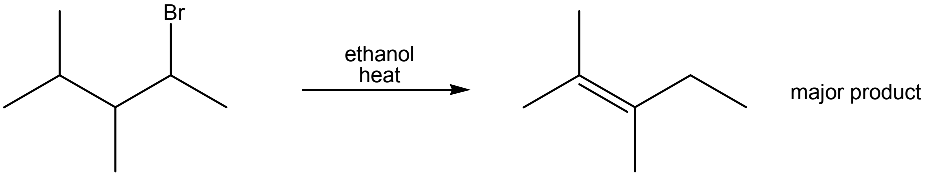


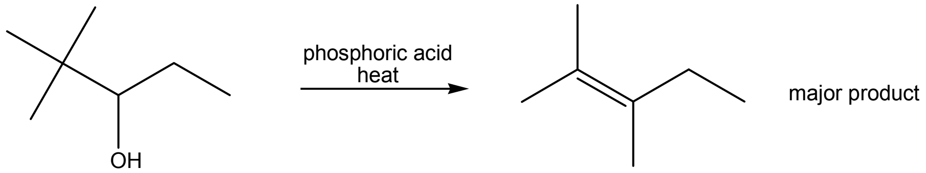
10. A lab technician accidentally spills some sodium iodide into the reaction mixture above. As a result a substitution product is observed along with the elimination product. Use curved arrows to show the mechanism of this side reaction, and draw the substitution product. (Is this substitution likely to be an S_N1 or an S_N2 reaction?)

11. Draw the products that result if *t*-butyl alcohol in the reaction in Exercise 9 is replaced with…
   a. 3-methyl-3-pentanol (three different alkene products).
   b. 3-methyl-3-hexanol (five different alkene products)
   c. Label the major product and the minor product in a).

12. When 3-methyl-2-pentanol is mixed with acid and heated, the same three products are produced as in a reaction with 3-methyl-3-pentanol, plus there is an additional product, 3-methyl-1-pentene.
   a. Show a mechanism that accounts for the product 3-methyl-1-pentene.
   b. Show a mechanism that accounts for the major product, *E*-3-methyl-2-pentene.
   c. Show a mechanism that accounts for the product 2-ethyl-1-butene.

13. Show a mechanism to account for the major product of each reaction below.





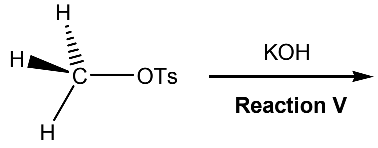
14. Read the assigned pages in the text, and do the assigned problems.

Exercises for Part B

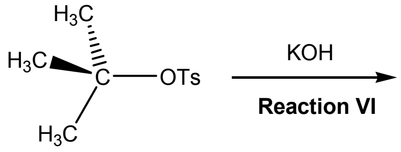
15. Use curved arrows to show the mechanism of each E2 and S_N2 reaction (leading to the major product of each reaction pathway) in Figure 14.7.

16. What is the major E2 product if hydroxide is replaced with *tert*-butoxide in Rxn IV in Figure 14.7?

17. Explain why only S_N2 (no E2) is observed in Reaction V.

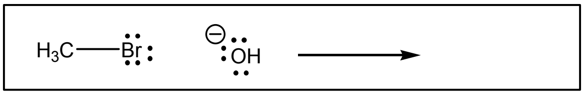


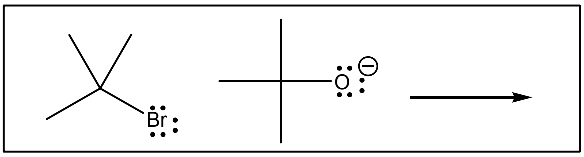
18. Explain why only E2 (no S_N2) is observed in Reaction VI.

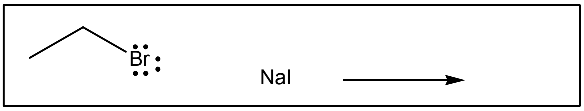


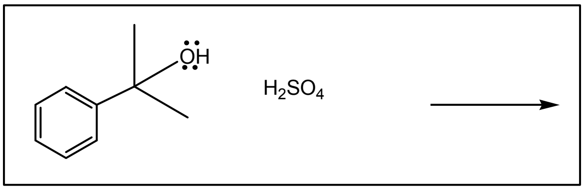
19. What is the definition of a strong base?

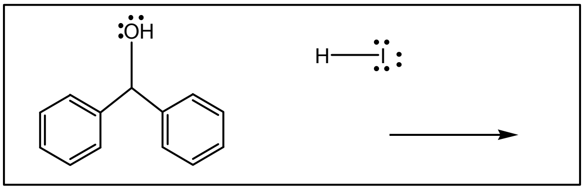
20. For many pairs of reactants, at least two of the mechanisms S_N1, S_N2, E1, and E2 are in competition with one another. Each of the following pairs is an exception to this trend in that it goes almost exclusively by one of these four reaction mechanisms. For each reaction…











   a. Decide which reaction mechanism is most likely for each box, and write S_N1, S_N2, E1 or E2 over the reaction arrow.

   b. Use curved arrows to show the mechanism, and draw the product/s.

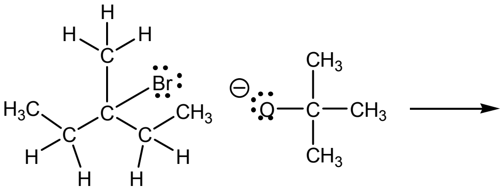
   c. Briefly explain why these starting materials can't or are unlikely to go by each of the other three reaction mechanisms.

21. Explain the following generalizations:

   a. You can't do E2 with a weak base.

   b. You can't do E1 with a strong base.

22. Use curved arrows to show the most likely mechanism and major product of this reaction.



a. Draw the transition state for the reaction above. Represent each partial bond using a dotted line, and show partial charges as δ–.

b. Is the major product of this reaction a Zaitsev or a Hofmann product?

23. In the laboratory, it is often impossible to avoid a mixture of substitution and elimination products. **Fill in the table with the phrases below without looking at the decision tree.**

Favored Mech.	**Base/Nuc**	**R—X**	**Rate dependent on [??]**	**Solvent**	**Temp**
S_N1					
S_N2					
E1					
E2					

Col. 2: Strong base; Weak base and poor nucleophile; Weak base and OK nucleophile; Good nucleophile

Col. 3: 2°, 3°, allylic, or benzylic only; 2°, 3°, allylic, or benzylic only AND must have H_β; methyl and 1° best but 2° OK; 1°, 2°, 3° allylic, and benzylic all OK but must have H_β

Col. 4: R–X only (two boxes); R–X and Base; R–X and Nucleophile

Col. 5: polar-protic required (two boxes); polar aprotic (two boxes)

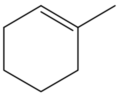
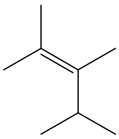
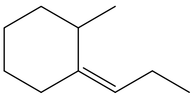
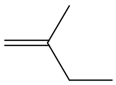
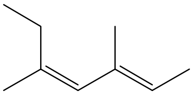
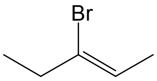
Col. 6: hot, cool

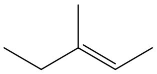
24. Agree or disagree with the following statements overheard during student discussions in class, and explain your reasoning.

    a. S_N1 and E1 cannot occur with a 1° leaving group

    b. S_N2 and E2 cannot occur with a 3° leaving group

25. Assign each double bond in the following molecules as E, Z, or *neither.*

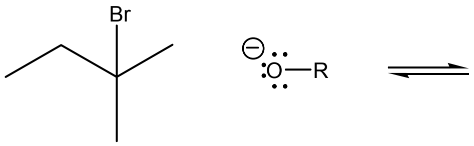







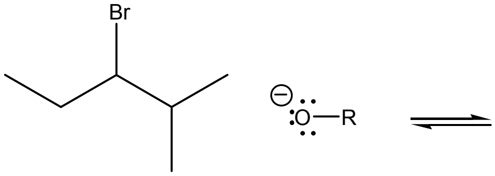


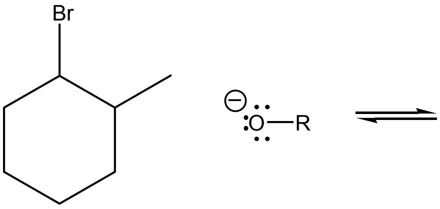
26. For each pair of reactants…

    a. Draw all possible E2 products.

    b. Circle the lowest potential energy product in each case.

i.


ii.


iii.


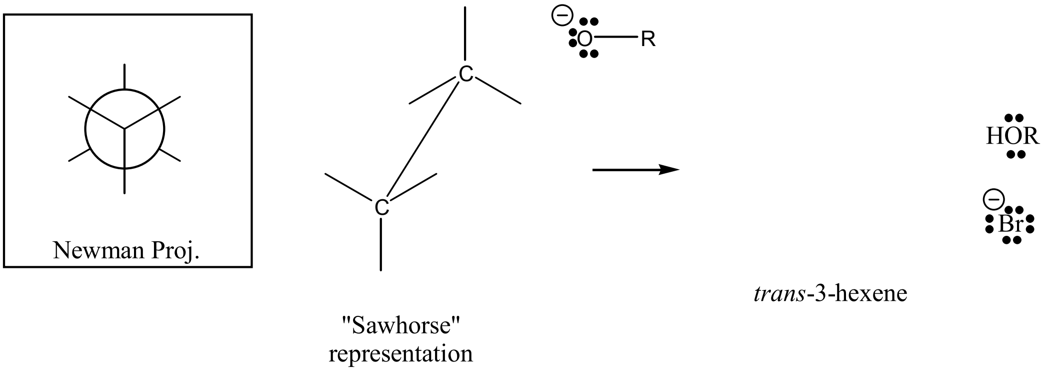
27. Take out a blank piece of paper, and **without consulting the decision tree** write down reagents/conditions that would yield… S_N2, S_N1, E1, or E2, respectively.

28. Take out a blank piece of paper, and try to generate from memory the decision tree for each methyl, primary, secondary, and tertiary leaving groups.

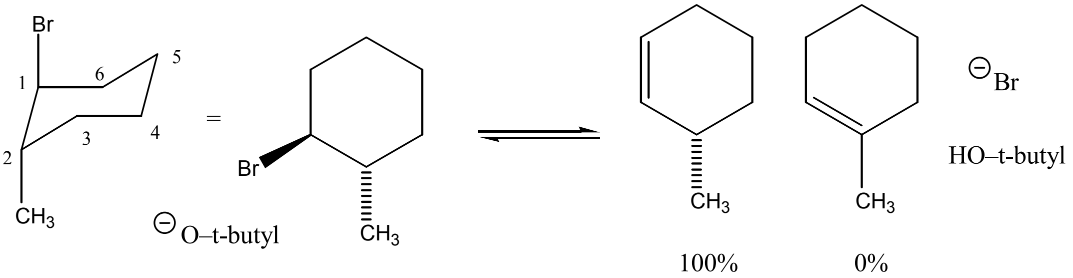
29. Read the assigned pages in the text, and do the assigned problems.

Exercises for Part C

30. Complete the following Newman and sawhorse representations of (S)-3-bromohexane showing a conformation that would give rise to ***trans*-3-hexene**. Also draw *trans*-3-hexene, and show the mechanism of formation using curved arrows.



31. Even though the tri-substituted alkene product on the right is lower in potential energy, only the di-substituted product is observed in the reaction below.



a. Draw two Newman Projections of the reactant, one sighting down the C_1–C_2 bond and the other sighting down the C_1–C_6 bond.

b. Use your Newman Projections as the basis for explaining why the di-substituted alkene is preferentially formed.

32. Which of the following true statements helps explain(s) the product distribution in CTQ 45? (More than one may help explain the distribution.)

   (1) The conformation leading to the *cis* product is less favorable than the conformation leading to the *trans* product.

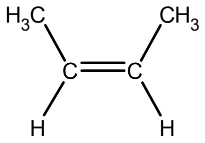
   (2) The methyl groups of the *trans* product are farther apart than in the *cis* product. This leads to less steric hindrance and therefore lower P.E. for the *trans* product.

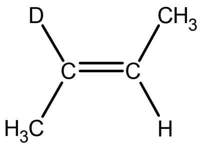
   (3) A terminal double bond (one at the end of a chain) is higher in potential energy then an internal double bond (one in the middle of a chain).

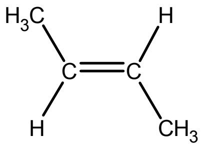
   (4) Heat favors elimination.

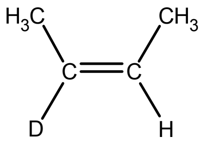
33. Name the configurational stereoisomer of 3-bromo-4-deuterohexane shown in CTQ 46.
    a. Draw a Newman projection of the enantiomer of this molecule in its lowest potential energy conformation (what is the name of this molecule?).
    b. Draw the major product of an E2 reaction involving this enantiomer.
    c. Draw a Newman projection of the configurational stereoisomer of 3-bromo-4-deuterohexane that will give *trans*-3-hexene as the major product.
    d. What is the name of this configurational stereoisomer that gives *trans*-3-hexene?
    e. What is the relationship between this molecule and the original molecule in CTQ 46?

34. Consider the four possible di-substituted E2 products below.







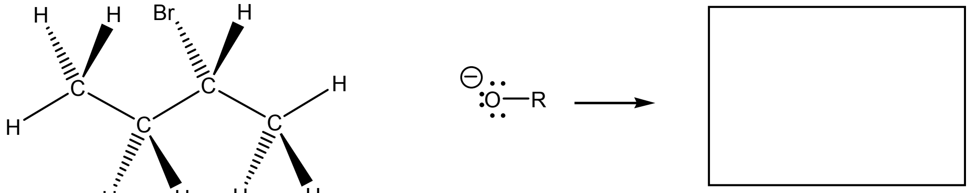


    a. Circle the two that could be produced by E2 reaction of (2S,3S)-2-bromo-3-deuterobutane.
    b. Mark one as the “major product” and one as the “minor product.”
    c. Draw a sawhorse representation of the conformation that would give rise to each of these two products.
    d. Draw and name the enantiomer of (2S,3S)-2-bromo-3-deuterobutane.
    e. Could E2 reaction with this configurational stereoisomer give rise to either of the two uncircled alkene products? If so, show the sawhorse representation of the conformation giving rise to each product.
    f. Draw AND NAME a diastereomer of 2-bromo-3-deuterobutane.
    g. Can this configurational stereoisomer give rise to the other two products? If so, show the sawhorse representation of the conformation giving rise to each product.

35. Draw an energy diagram for the reaction shown in CTQ 47, and put points on the diagram labeled 1to 4 to correspond with orbital pictures 1 to 4 in CTQ 47.

36. In terms of orbitals, explain why an E2 reaction cannot occur via removal of an H that is gauche to the leaving group—and why the H must be anti. *Hint*: Sketch an orbital drawing of the transition state removing an H gauche to Br. Will the newly forming *p* orbitals be aligned in a way that can immediately form a double bond?

37. On the following drawing of (R)-2-bromobutane…



1-butene

a. Circle any H that, if removed in an E2, would give *cis*-2-butene, and label it "**gives *cis*.**"

b. Circle any H that, if removed in an E2, would give *trans*-2-butene, and label it "**gives *trans*.**"

c. Draw 1-butene in the box provided.

d. Put a triangle around any H that, if removed, would give rise to 1-butene.

e. Give an example of an R group that would give 1-butene as the major product in this reaction.

f. Use curved arrows to show the mechanism of an E2 reaction leading to 1-butene.

g. A student predicts that the ratio of *trans*-2-butene to 1-butene should be 1:3 in the final product mixture. Explain how she came up with the ratio 1:3, and explain the **flaw** in her reasoning.

38. Read the assigned pages in the text, and do the assigned problems.

The Big Picture

Everyone finds this activity challenging. It takes a week or two of hard work, sifting through substitution and elimination reactions, to finally feel comfortable with the decision tree in Memorization Task 14.6. Do lots of problems, and constantly ask yourself or your study partner "why" for each branch point of the decision tree. (The only concept we are asking you to memorize without an explanation is that heat favors elimination—though this makes sense too, if you wish to look it up.) The others should all make sense after a careful study of ChemActivities 13 Parts A-D and ChemActivity 14 Parts A and B.

ChemActivity 14 Part C is not to be underestimated. Some of the most challenging stereochemistry questions I have seen on exams are some variation on Exercises 31, 33, 34, or 37. As with many questions involving stereochemistry, start by building a model. These are five minutes well spent as they will save you much frustration in solving these four questions.

Common Points of Confusion

- Do not blindly memorize the associations: tertiary leaving group → S_N1 and E1; and primary leaving group → S_N2 and E2. Only the first three-quarters of this rule are valid. Tertiary electrophiles cannot undergo S_N2 (too hindered), and (ordinary) primary and methyl electrophiles cannot undergo S_N1 or E1 (unfavorable carbocations). But the rule DOES NOT work for E2. Tertiary electrophiles commonly undergo **E2**.

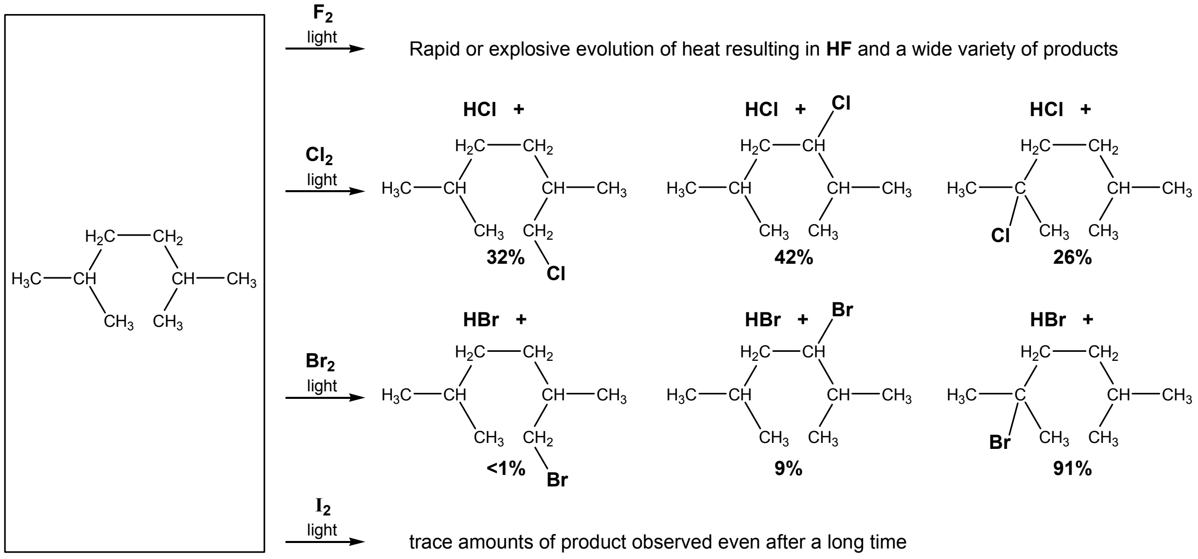
- Some students assume (incorrectly) that an E1 reaction with bicarbonate or bisulfate (the weak conjugate bases of carbonic and sulfuric acids, respectively) will produce a Hofmann product (less substituted alkene) because these weak bases are large. While this is a logical conclusion, it does not happen. E1 reactions always obey **Zaitsev's rule** (give the most substituted alkene product), regardless of the size of the base. This is because E1 reactions are **reversible**. In essence, E1 products tend to "undo" themselves, but the lowest P.E. product is most likely to persist.

ChemActivity 15: Radical Reactions

PART A: RADICAL HALOGENATION OF ALKANES

(How can we add a functional group to an un-functionalized alkane?)

Model 1: Radical Halogenation of Alkanes


F2
light
Rapid or explosive evolution of heat resulting in HF and a wide variety of products
Cl2
light
HCl +
32%
HCl +
42%
HCl +
26%
Br2
light
HBr +
<1%
HBr +
9%
HBr +
91%
I2
light
trace amounts of product observed even after a long time

Critical Thinking Questions

1. (E) Describe the transformation in the reactions in Model 1. (What is replaced by what?)

2. (E) Which replacement of an H with a halogen (F, Cl, Br, or I) is fastest? …which is slowest?

Memorization Task 15.1: Relative rates of halogenation: $F_2 >> Cl_2 > Br_2 >> I_2$

Fluorination of an alkane is dangerously fast. Iodination is so slow as to be impractical. Only chlorination and bromination are commonly used in laboratories.

3. Each reaction in Model 1 gives a mixture of products. Based on the percentage of each product, what type of H is **MOST** likely to be replaced with Br? (Choose from [1° H], [2° H], or [3° H].)

4. Because of symmetry, the starting material in Model 1 (2,5-dimethylhexane) has only one type of 1° H, one type of 2° H, and 1 type of 3° H. What is the ratio of the number of [1°]: [2°]: [3°] H's?

5. Explain how the data in Model 1 support this statement: "If there were an alkane with an equal number of 1° and 3° H's, Cl would be about **five times more likely** to replace a 3° H than a 1° H." (*Hint*: In 2,5-dimethylhexane how many more 1° H's are available for reaction compared to 3° H's?)

Memorization Task 15.2: H-type selection preferences for radical halogenation reactions

Radical halogen reactions preferentially replace an H on an alkane according to the following order:

Benzylic > Allylic > Tertiary (3^{o}) > Secondary (2^{o}) > Primary (1^{o}) > Methyl (0^{o})

A benzylic H is an H on a benzylic C (= C next to a benzene ring). An allylic H is an H on an allylic C (= C next to a π bond).

Critical Thinking Questions

6. According to the data in Model 1, which halogen (Cl or Br) is more **selective** (choosy) when replacing an H on an alkane? Explain your reasoning.

7. Circle one answer that best fits the data in Model 1: "Bromine is (**two times**, **five times**, **10 times**, **20 times**, or **100 times**) more likely to replace an individual 3^{o} H than a 2^{o} H."

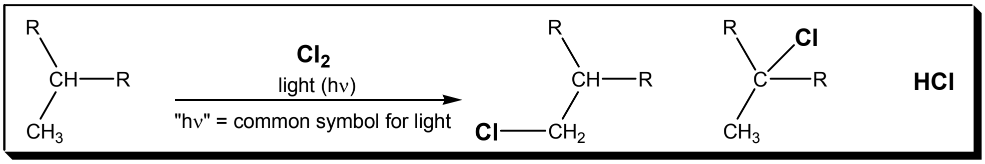
8. (Check your work.) Are your answers to the previous three CTQ's consistent with the data in Memorization Task 15.3?

Memorization Task 15.3: Approximate selectivities of Cl_2 and Br_2 in radical halogenations

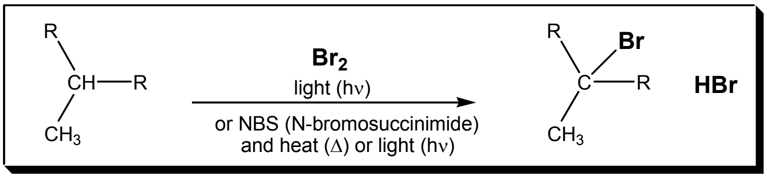
Halogen (X)	X sub. for H in a **1°** Position	X sub. for a H in a **2°** Position	X sub. for a H in a **3°** Position	X sub. for a H in **allylic** Position	X sub. for a H in **benzylic** Position
Cl	1	4	5	similar to 3^{o}	
Br	1	100	2000	>> 3^{o}	>> allylic

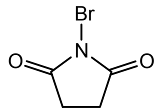
While you many not need to memorize the exact selectivities above, you should memorize that Br is highly selective while Cl does not distinguish much between 2^{o}, 3^{o}, allylic and benzylic H's (though it shows some preference for these over 1^{o} H's).

Synthetic Transformation 15.1: Radical Chlorination of an Alkane



Synthetic Transformation 15.2: Radical Bromination of an Alkane





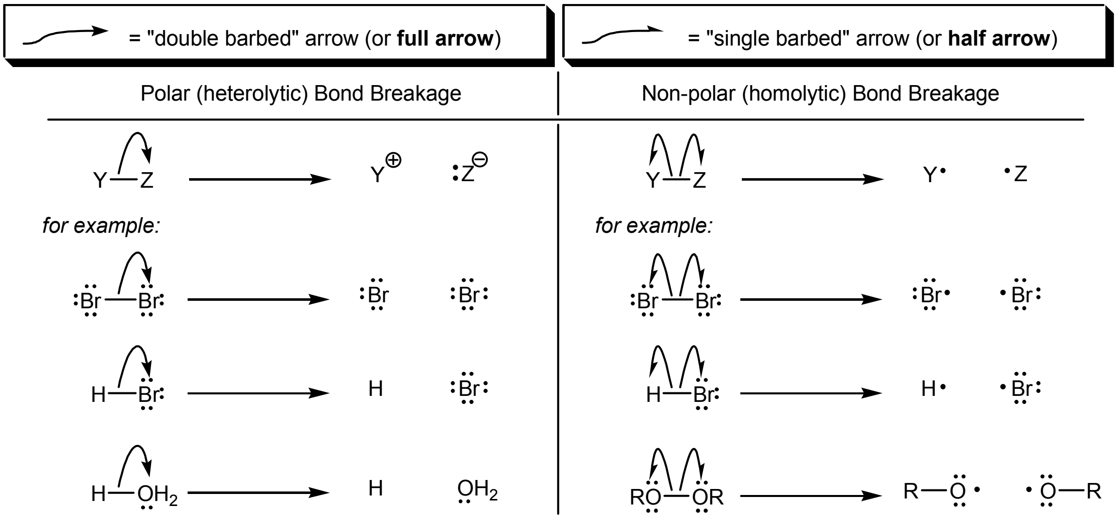
a reagent that generates Br radicals, the active species in a radical bromination

N-bromosuccinimide

Model 2: Polar and NonPolar Bond Breakage

Mechanisms in this course outside of this chapter involve **polar bond breakage** in which the two electrons comprising a bond move together as a pair when the bond breaks, generating + and – charges.

radical = species with an unpaired electron (Radicals result from nonpolar bond breakage.)


= "double barbed" arrow (or **full arrow**)
= "single barbed" arrow (or **half arrow**)
Polar (heterolytic) Bond Breakage
Non-polar (homolytic) Bond Breakage
Y—Z
Y⊕ :Z⊖
Y• •Z
for example:
:Br—Br:
H—Br:
H—OH2
H
OH2
H•
RO—OR
R—O•
•O—R

Critical Thinking Questions

9. Add formal charges, if necessary, to the examples in Model 2.

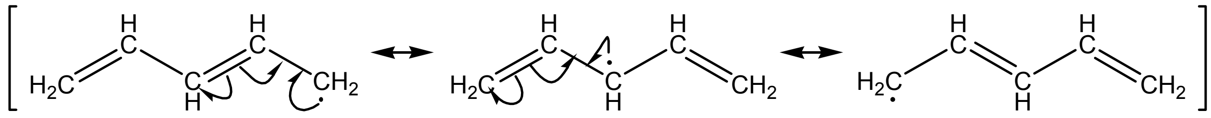
10. A **double-barb arrow** depicts the movement of a pair of electrons. What does a **single-barb arrow** depict?

11. Circle all **radical species** in Model 2.

Memorization Task 15.3: Radical Potential Energies

highest P.E. •H •CH_3 •1° •2° •3° •allylic •benzylic •X (halogen) **lowest P.E.**

Memorization Task 15.4: Radicals can be resonance stabilized (but do not rearrange)



Curved single-barb arrows are used to generate resonance structures of an allylic or benzylic radical.

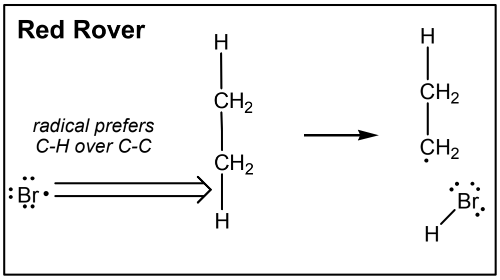
Critical Thinking Questions

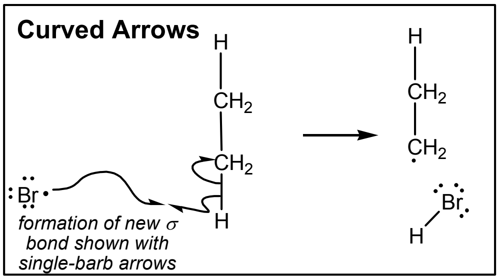
12. In what ways are radicals similar to carbocations? In what ways are they different?

Model 3: "Red-Rover Red-Rover, send Radical right over!"

Radical reactions behave similarly to the school-yard game "Red-Rover." However, unlike the kid's version of Red-Rover, in the radical version the radical bonds to one of the two atoms it splits apart.

Recall from oxidation reactions that a C—H bond is easier to break than a C—C bond.

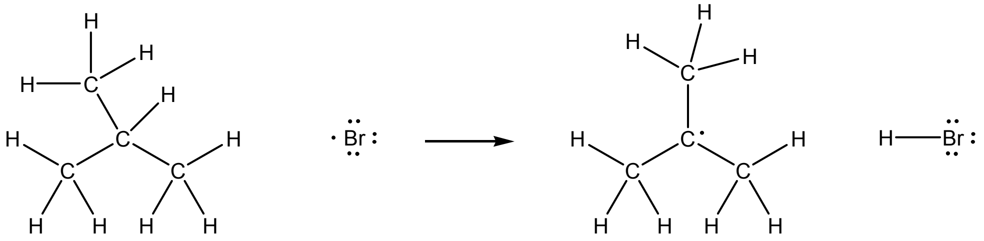




Critical Thinking Questions

13. Construct an explanation for why the Br radical in Model 3 stuck to the H instead of the C. (*Hint*: What radical would be produced if the Br radical had stuck to the C instead?)

14. Use curved single-barb arrows to show the mechanism of the following step in a radical reaction.

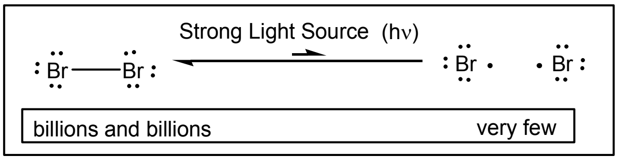


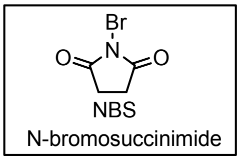
15. Construct an explanation for why the Br radical in the previous question broke that particular C—H bond even though there are nine C—H bonds of the other type.

Model 4: Sources of Cl and Br Radicals

When Cl_2 or Br_2 is exposed to intense light (hν) a small number of Cl or Br radicals are produced.

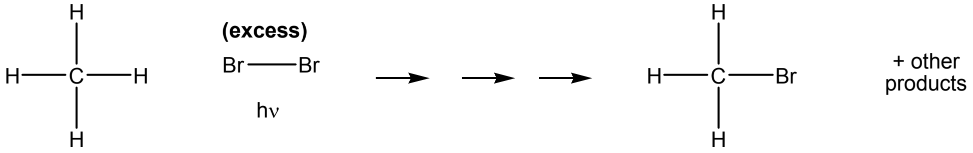
Alternatively, exposing **NBS (N-bromosuccinimide)** to heat or light will generate Br_2 and radicals.





Critical Thinking Questions

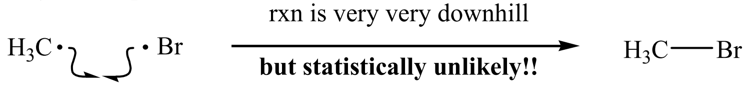
16. Use curved single-barb arrows to show a **multi-step** mechanism for the following reaction



Model 5: Collision Statistics

A reaction between two radicals may seem very likely from an energy standpoint because, in such a reaction, two high-potential-energy species combine to form one low-potential-energy species.

for example:



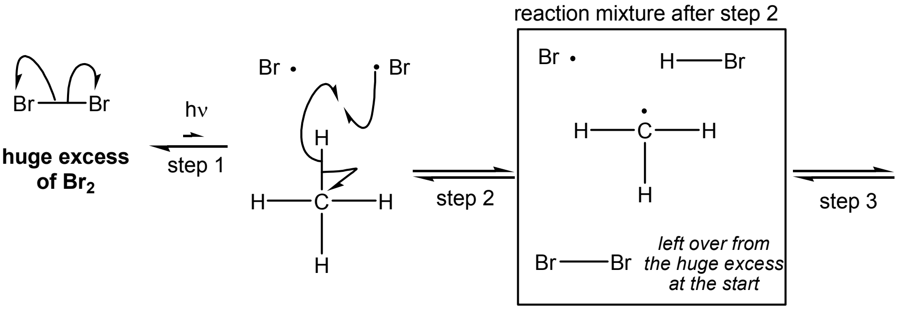
However, radicals are **so** high in energy that they react with anything they “bump into.” This means a radical has a short life-span and usually does not have time to “find” another radical.

Critical Thinking Questions

17. Picture the old Veterans Stadium in Philadelphia filled to capacity with 62,382 people. Eagles fans are *normally* peaceful folks, but on this day there are five violently reactive fans in the stadium that will start a fight with the first person they bump into (getting themselves thrown into Veterans’ in-house jail). Assume the violent fans are dispersed randomly in the crowd. What are the chances that two of the five "violently reactive fans" get in a fight with one another?

18. Based on the information in Model 5, circle any step in your mechanism at the top of the page that has a low probability of occurring, and explain your reasoning.

19. The first two steps of the mechanism from the previous page are drawn for you below.



a. Methyl radical ($\cdot CH_3$) is like the "fighter" in the stadium analogy. It will react with the first bond it bumps into. What is the most prevalent species in the reaction mixture after step 2?

b. Show the statistically most likely Step 3 in the mechanism above. **Note: This step leads to formation of a CH_3Br, but there are also radical species left over at the end of step 3.**

Model 6: The Three Parts of a Domino (or Radical) Chain Reaction

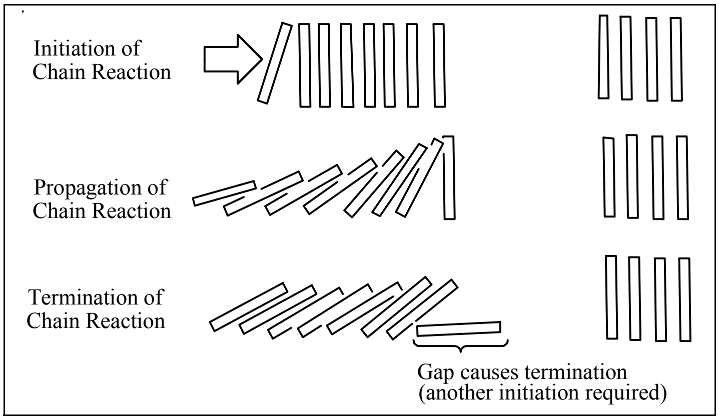

Initiation of Chain Reaction
Propagation of Chain Reaction
Termination of Chain Reaction
Gap causes termination (another initiation required)

Figure 15.1: Domino Chain Reaction

A **radical chain reaction** is a reaction with the following parts:

I. **Initiation** = net generation of radicals

II. **Propagation** = one radical consumed; one radical produced

III. **Termination** = net consumption of radicals

Critical Thinking Questions

20. The mechanism at the top of the page is a radical chain reaction.

a. Identify the **initiation step**.

b. Identify the two **propagation steps**.

c. A collision between two radicals is unlikely, but it does happen every once in awhile. Eventually such reactions will stop the chain reaction. List at least two possible **chain termination steps** (they don’t have to lead to H_3C-Br).

PART B: ANTI-MARKOVNIKOV ADDITION OF HBr TO A π BOND

(Why does the regiochemistry of Br differ in radical vs. polar addition of HBr to an alkene?)

Model 7: Review of Reactions of Alkenes with Br_2 and HBr

15.2 (from Part A)

9.1 (from CA 9)

8.4 (from CA 8)

8.5 (from CA 8)

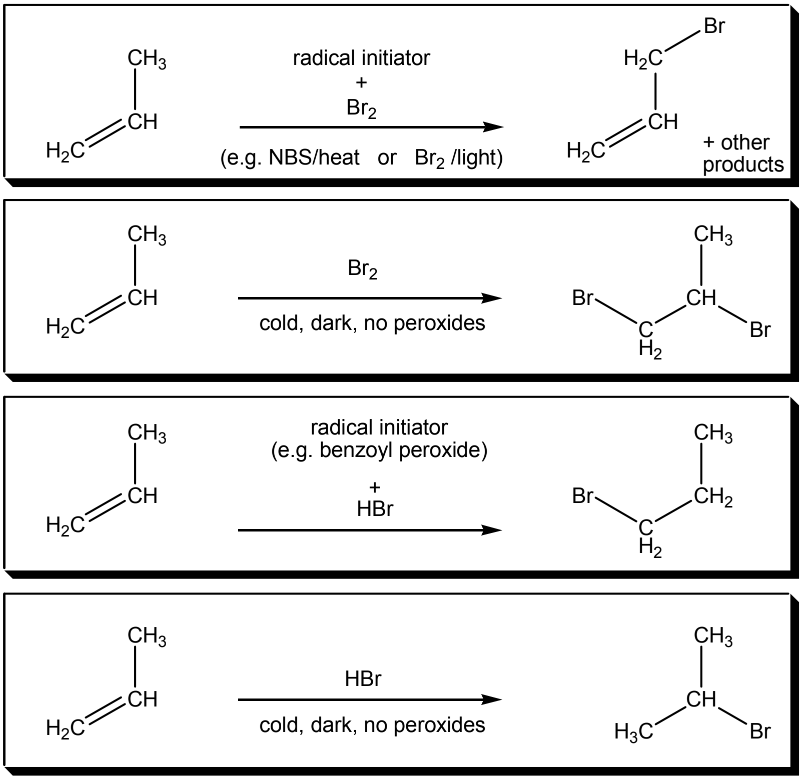


Figure 15.2: Reaction of an alkene with Br_2 or HBr under radical or polar conditions

Critical Thinking Questions

21. Label each reaction in Model 7 **radical** or **polar**.

22. Label each reaction in Model 7 **Markov., anti-Markov.,** or **neither** (use each term at least once).

Information

As with σ bonds, a radical can crash into a π bond, break it, and bond to one of the participants (as shown in Figure 15.3).

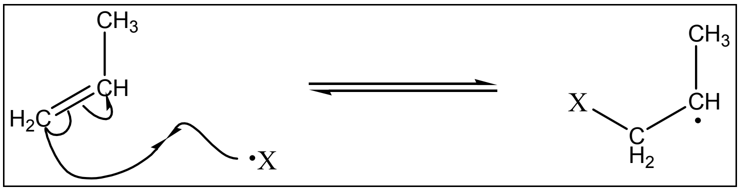
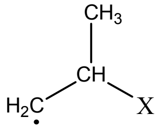
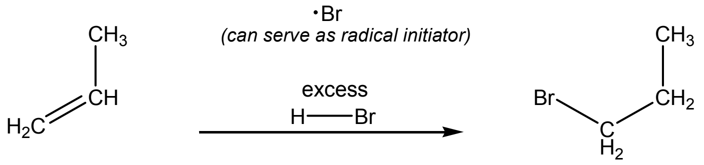


Figure 15.3: Mechanism of a radical reacting with a π bond

23. Explain why the radical shown in Figure 15.3 is formed instead of this radical →



24. Use curved single-barb arrows to show two propagation steps leading to the product shown. (You need not show any termination steps.)

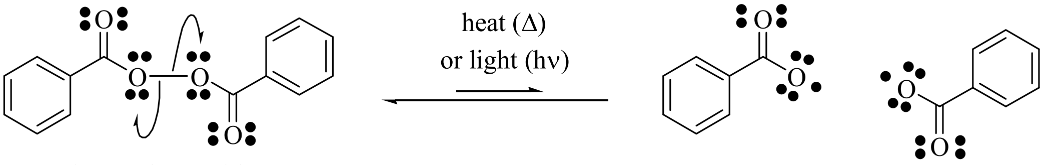


Model 8: Peroxides as Radical Chain Reaction Initiators

Previously we have seen that a strong light source can be used to initiate a radical chain reaction by breaking a Br—Br bond and generating Br radicals.

This method is effective only when there is a high concentration of Br_2 in solution, but the reaction at the top of the page works only when the concentration of HBr is high compared to Br_2.

To keep the Br_2 concentration low, **peroxide** is used as **radical initiator** because the O-O bond is easy to break. Benzoyl peroxide is a common radical initiator.



benzoyl peroxide

Bond dissociation energy (BDE) is the amount of energy required to break a bond in a nonpolar fashion ("**homolytic bond cleavage**"), with one electron going to each of the two atoms involved in the bond. The BDE of the O–O bond of…

hydrogen peroxide (HO–OH) = 51 kcal/mole (kcal = a measure of energy)

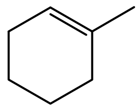
benzoyl peroxide = 18 kcal/mole

Critical Thinking Questions

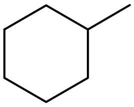
25. (E) Which is easier to break, the O–O bond of **hydrogen peroxide** or **benzoyl peroxide**?

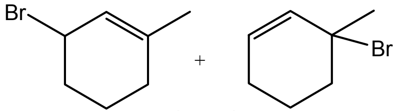
26. Construct an explanation for why this is the case. (*Hint*: See Memorization Task 15.4.)

27. (On a separate piece of paper) Design a synthesis of each of the following target molecules starting from methylcyclohexene and any noncyclic reagents.

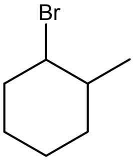


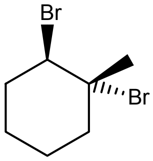
methylcyclohexene



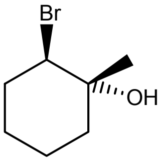


+ other products

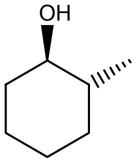




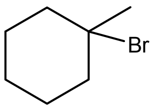
+ enantiomer

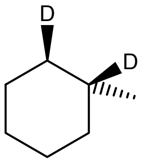


+ enantiomer

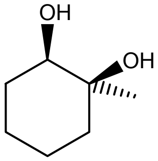


+ enantiomer

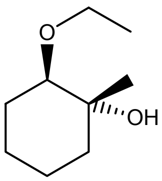




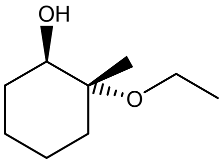
+ enantiomer



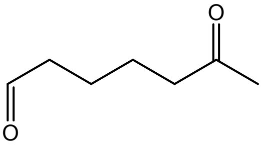
+ enantiomer

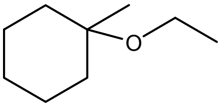


+ enantiomer



+ enantiomer

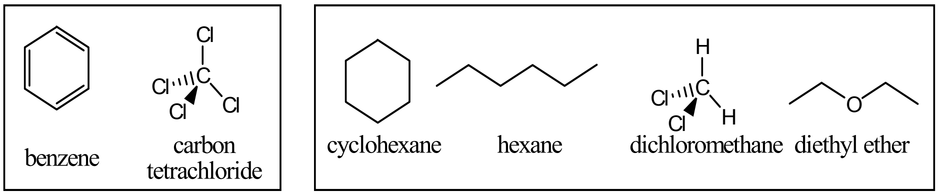




Exercises for Part A

1. Along with the methyl radical, there is a Br radical in the box in CTQ 19. What happens if the Br radical reacts with the most abundant species in the reaction mixture (Br-Br)? Draw this reaction, and explain why it is not very interesting.

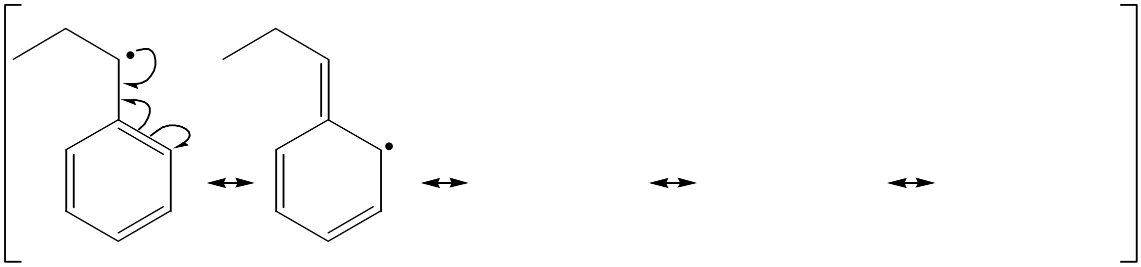
2. Construct an explanation for why the solvents on the left are suitable for radical halogenation reactions, but the solvents on the right are not.

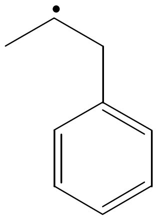


suitable solvents **NOT suitable solvents**

3. Give an example of each of the following: primary radical, secondary radical, tertiary radical, methyl radical, benzylic radical, allylic radical.

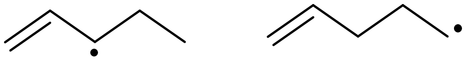
4. Consider the partial resonance representation of a benzylic radical species.





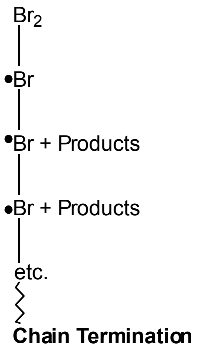
   a. Use curved half-arrows to generate the other three resonance structures of the radical above.
   b. Explain why a benzylic radical is much lower in potential energy than the radical drawn at right.
   c. Can the radical at right rearrange to become a benzylic radical?

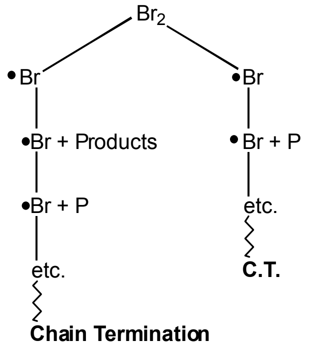
5. Circle the species below that is lower in potential energy.

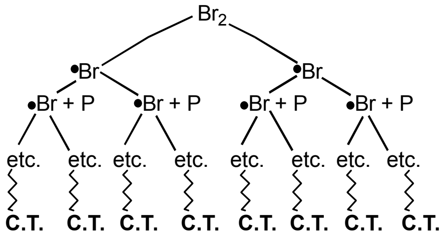


   a. Construct an explanation for your choice including drawing at least one other structure.
   b. Which one of these radicals is an allylic radical?
   c. Draw an allylic carbocation, and summarize the similarities and differences between an allylic radical and an allylic carbocation.

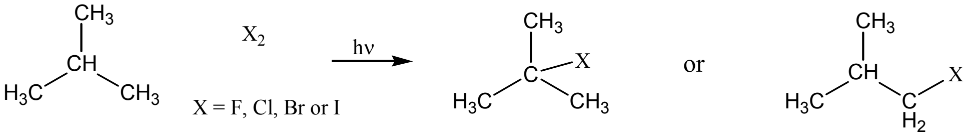
6. Which of the following diagrams best tracks the products formed from a single initiation event (breaking apart of one Br_2 molecule) in a **radical chain reaction**?







7. Use curved single-barb arrows to show an initiation step and propagation steps leading to each of the following products.



8. Summarize the effect of each factor on the ratio of the two products shown above.

   a. The type of H (benzylic, allylic, 3°, 2°, 1° or methyl).

   b. The number of H's of a given type.

   c. The identity of X (F, Cl, Br, or I).

9. Explain why, for the example above, you would expect a **1:9** ratio of 3° to 1° H substitution products if a 3° radical had about the same potential energy as a 1° radical.

10. But a 3° radical does not have the same potential energy as a 1° radical.

    a. When X = Cl, how many times more favorable is a 3° radical than a 1° radical intermediate?

    b. What ratio of 3° to 1° products is expected for Exercise 7 when X = Cl? X = Br?

11. Fill in the blank with F_2, Cl_2, Br_2 or I_2

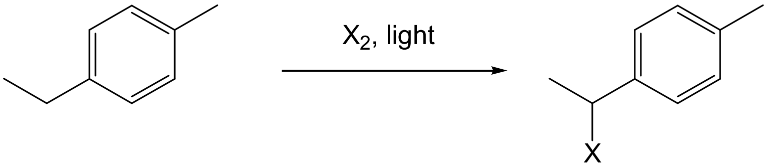
    a. Radical halogenation with ____ is unselective, violent and dangerous, limiting the usefulness of this reaction in organic synthesis.

    b. Radical halogenation with ____is so slow as to be useless in organic synthesis

    c. Radical halogenation with ____is just right to be useful in organic synthesis because the rate is manageable, and the reactions are very selective.

    d. Radical halogenation with ____ is often used in the laboratory to halogenate molecules with only one kind of H (e.g., cyclohexane).

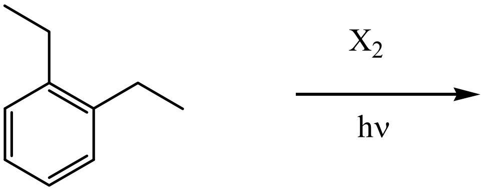
12. Consider the following synthesis of the alkyl halide shown below.



a. A student chooses Cl_2 as the halogen and gets a mixture of three different products. Draw them, and estimate the approximate product ratio.

b. Explain why replacing Cl_2 with a different halogen (specify which one) would give a much better yield of the desired product.

13. Consider the following reaction.



a. There are two different H's in this molecule that can be replaced by X. Add them to the drawing above, and label them H_a and H_b.

b. There are two different H's on this molecule that will not react with X radical. Label them H_c and H_d.

c. Specify whether H_a and H_b are primary, secondary, tertiary, allylic or benzylic.

d. Calculate the relative amounts of each of the two different products when the reaction is run with Cl_2.

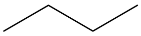
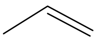
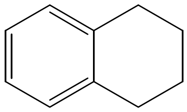
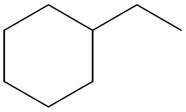
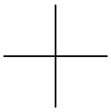
e. Calculate the relative amounts of each of the two different products when the reaction is run with Br_2.

f. Which reaction is more selective: the reaction with **Cl_2** or **Br_2**? (Circle one, and explain your reasoning).

14. Draw all possible radical halogenation products using X_2 and light (Mark each chiral center with an * to indicate R/S configurational stereoisomers are possible).

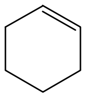
a. Estimate the ratio of the products if X = Cl_2

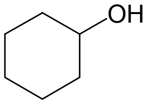
b. Estimate the ratio of the products if X = Br_2

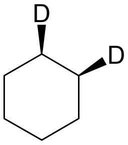






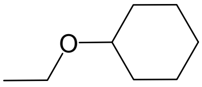
15. S-3-methylhexane undergoes radical bromination to form a 1:1 ratio of two major products.
    a. Draw both major products.
    b. Assign R and S to each chiral center.
    c. What term describes the relationship between these two products?

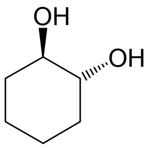
16. Design a synthesis of each of the following target molecules starting from cyclohexane.



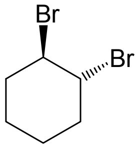




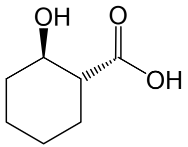




+ enantiomer

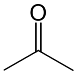


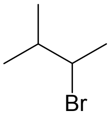
+ enantiomer

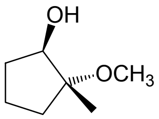


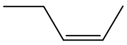
+ enantiomer

17. Design a synthesis of each of the following target molecules starting from any alkane.

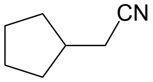


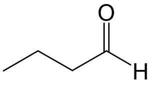


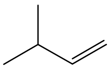




cis only



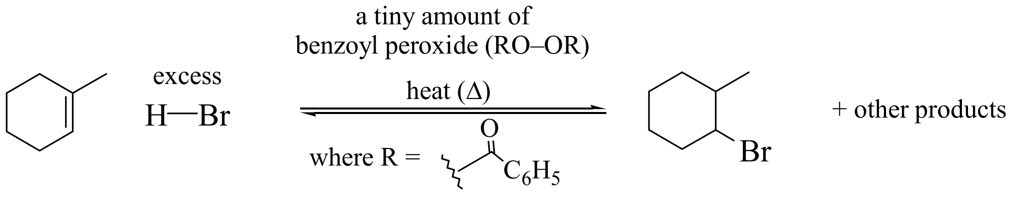




18. Read the assigned pages in the text, and do the assigned problems.

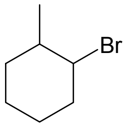
Exercises for Part B

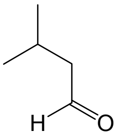
19. Show a mechanism for the following reaction including…

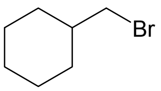


    a. an initiation step.
    b. propagation steps that lead to the product shown.
    c. two possible termination steps.

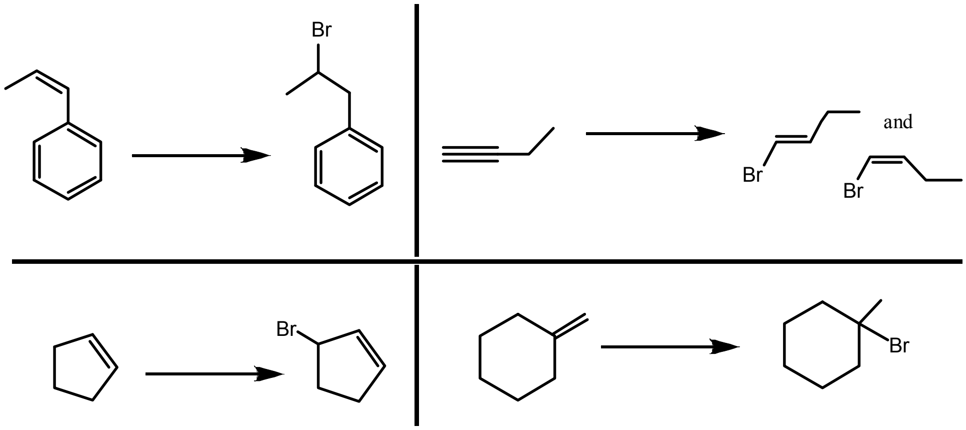
20. Design a synthesis of the following target molecules beginning with any alkane.







21. Over each reaction arrow, write in reagents that would give the product shown.



22. Show a mechanism for each reaction in the previous question.

23. Oxygen—oxygen single bonds are relatively easy to break. Construct an explanation for why benzoyl peroxide has an especially small B.D.E. compared to other peroxides.

24. Read the assigned pages in the text, and do the assigned problems.

The Big Picture

There are two basic types of reactions: polar reactions and radical reactions. This course focuses on polar reactions because these are better understood and easier to diagram using curved arrows. Radical reactions are just as common, but are not emphasized in organic chemistry courses because they are complicated, poorly understood, and often lead to products via a wide array of competing mechanisms. This chapter only scratches the surface when it explores the mechanisms of several well-behaved radical reactions. We will see other radical reactions throughout this book (e.g., oxidation and reduction reactions), but we will not discuss their mechanisms. In fact, most reactions in this book that are presented without a mechanism are radical reactions.

Common Points of Confusion

- It is critical that you keep straight the large number of very similar reactions (see Model 7). Note cards are the way to go from here on out, even if you have not been using them so far. See the Exercises for Part B of ChemActivity 8 for advice on how to make the most of note cards.
- Two reaction types that are commonly confused with one another are 8.4/8.5—addition of HBr to an alkene (Markovikov or anti-Markovnikov), and 15.2—radical halogenation using NBS or Br_2 and light. This is especially confusing when substituting for an allylic H on an alkene.
- You may see a reagent such as… "HBr, cold, dark, no peroxides." The purpose of stipulating the temperature and conditions is simply to rule out the possibility of a radical reaction. Prior to this activity, this reaction was listed simply as HBr (Markov. addition of H and Br).

ChemActivity 16: Synthesis Workshop 1

PART A: RETROSYNTHESIS

(How can thinking backwards help me solve a synthesis problem?)

Model 1: Introduction to Multi-step Organic Synthesis

The main work of most organic chemists is building new molecules for use as everything from food additives to materials for the space shuttle. A large portion of this work is focused on drug synthesis.

The end product of a synthesis is called a **target molecule**. Chemists rarely "hit" the target on the first try. In fact, a team of chemists may spend months or years trying to synthesize a particular molecule.

The total synthesis of Vitamin B12 led by Robert Woodward of Harvard University in the 1960s and 70s involved hundreds of graduate students and took over a decade. This amazing accomplishment ushered in the modern era of synthetic organic chemistry and convinced many that synthesis of any target was possible given enough time and resources.

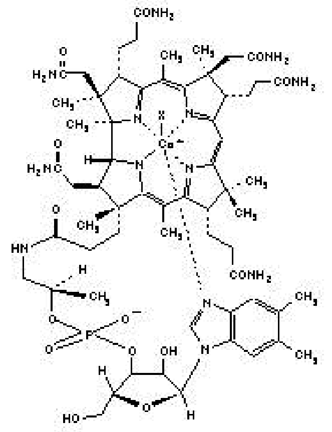
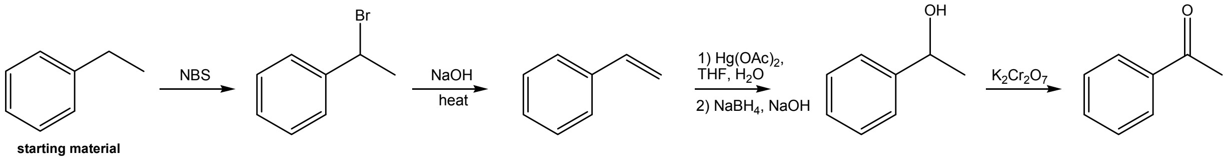


Figure 16.1: Vitamin B12

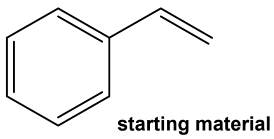
Our exploration of synthesis will focus on simple targets that are often **commercially available**. If we were really trying to obtain such a molecule we would order it from a chemical company with a facility for making it in large batches, allowing them to sell it for much less than it would cost us to make it in the laboratory.

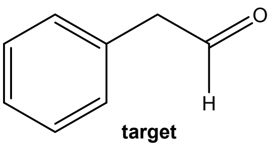
Shown below is an example of a simple, linear, multi-step synthesis.



Critical Thinking Questions

1. (E) Label the **target molecule** in the multi-step synthesis above.
2. Design a synthesis of the following target from the starting material.





Model 2: Retrosynthesis (Thinking Backwards)

Organic chemists use a process called retrosynthesis to "think backwards" from the target and figure out what **commercially available starting materials** are needed to make this target.

To solve the synthesis problem below using retrosynthesis you would start by asking yourself the question: "What molecules can be transformed into 2-bromo-3-methylbutane (**4**) in one synthetic step?" These molecules are called **precursors** of molecule **4**.

By convention, a **retrosynthesis arrow** is drawn from a molecule to its precursor (as shown below).

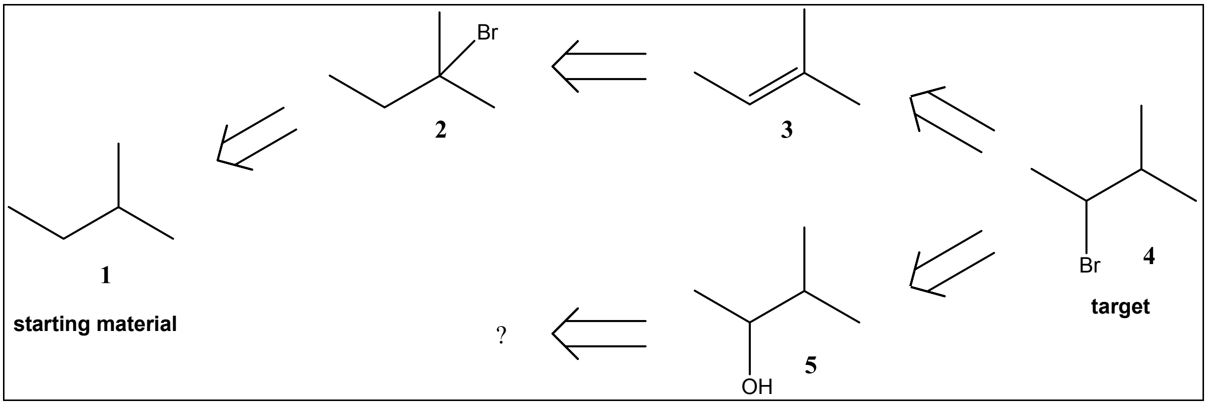


Figure 16.2: Retrosynthetic analysis of the target 2-bromo-3-methylbutane (4)

Critical Thinking Questions

3. (E) Identify the retrosynthesis arrows in Figure 16.2.

4. (E) Label the "precursors of target **4**" shown in Figure 16.2.

5. (E) Label the "**precursor** of molecule **3**" shown in Figure 16.2.

6. What reagents will transform **3** into **4**? (Draw a reaction arrow from **3** to **4**, and write these reagents above it.).

7. What reagents will transform **5** into **4**? (Draw a reaction arrow from **4** to **5**, and write these reagents above it.).

8. Are there reagents that will transform **1** into **5** in two or fewer synthetic steps?

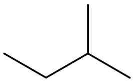
9. Is your answer to the previous question consistent with the fact that the preferred route from **1** to **4** does not involve **5**?

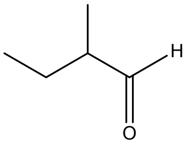
10. You can deduce the structure of **2** by thinking of a precursor of **3**. Or, if the starting material is given, you can work forward one step from the beginning. This is especially easy when the starting material is an alkane because we have learned only one type of reaction that applies to alkanes. Draw reaction arrows from **1** to **2**, and from **2** to **3**, and write reagents above them.

Memorization Task 16.1: When starting with an alkane, the 1st step = radical halogenation.

Critical Thinking Questions

11. Use retrosynthesis to design a synthetic pathway from the starting material to the product.





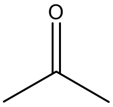
12. In the previous synthesis problem, did any carbon atoms need to be added to the starting material to make the product?

13. In the next synthesis problem, do any carbon atoms need to be added to the starting material to make the product?

14. Design a synthesis of the following target using the starting material and any reagents with one or fewer carbon atoms. (Work for five minutes on this question, then go onto the next section, which walks you part of the way through this problem.)

$HC{\equiv}CH$

starting material

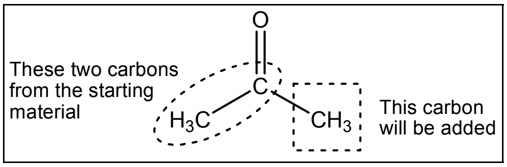


target

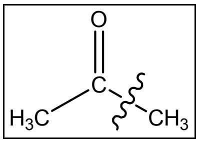
Model 3: Assembly of the Carbon Backbone

A key part of any synthesis is assembly of the **carbon backbone**. In the previous question the starting material has a two-carbon backbone, but the product has a three-carbon backbone.

A retrosynthetic analysis of this problem starts by deciding which two carbons in the product will come from the starting material. (In this case, because of symmetry, it does not matter if you choose the right two or left two.)


These two carbons from the starting material
O
C
H3C
CH3
This carbon will be added

During this synthesis we have to make a new carbon-carbon bond. For our retrosynthetic analysis (going backwards) we "cut" this new bond with a squiggly line to make two pieces. As you will see on the next page, **the challenge is to make these pieces and then make them bond them together**.



We know from our analysis on the previous page that at some point in this synthesis we must bond a two-carbon piece together with a one-carbon piece.

An easy way to make these pieces come together is for one piece to have some + charge and the other piece to have some – charge.

If we could magically create a perfect pair of reagents they would look like one of pairs in the boxes below. Unfortunately, no real molecule looks exactly like any of these pieces.

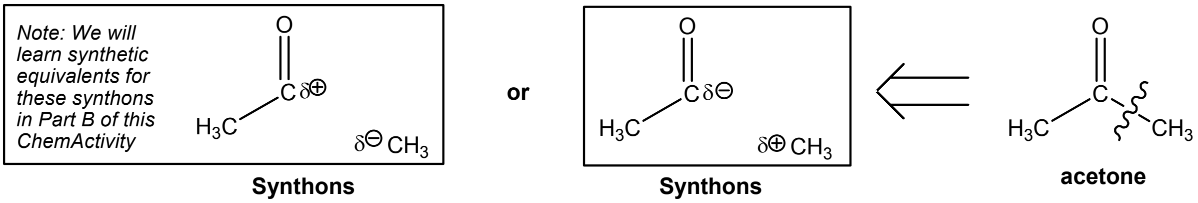

Note: We will learn synthetic equivalents for these synthons in Part B of this ChemActivity
O
C δ⊕
H3C
δ⊖ CH3
Synthons
or
O
C δ⊖
H3C
δ⊕ CH3
Synthons
O
C
H3C
CH3
acetone

Figure 16.3: Two pairs of synthons for making the target acetone

Term Introduction: Synthon = idealized (not real) positive or negative reactant

Synthons (see Figure 16.3) are not real reagents, but we can often find real reagents that behave like a given **synthon**. A reagent that behaves like a synthon is called a **synthetic equivalent** of that synthon.

Critical Thinking Questions

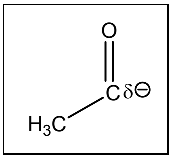
15. (E) What is the difference between the pair of synthons in the left and right boxes of Fig. 16.3?

16. Which one of the following reagents is NOT a **synthetic equivalent** of the synthon $H_3C^{\delta+}$?

$Br—CH_3$ $Cl—CH_3$ $I—CH_3$ $H—CH_3$ $TsO—CH_3$

Synthesis Tip 1: Focus on assembling the carbon backbone

It is often impossible to find an *exact* synthetic equivalent of a synthon with O, N, X or other "heteroatoms" (such as the synthon at right). In such cases, focus on first assembling the correct carbon backbone, then worry about attaching the heteroatoms.



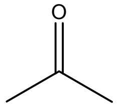
17. In this case, we need a three-carbon backbone. Draw a two-carbon nucleophile that can be made in one synthetic step from the starting material, acetylene. (Check your work: See Synth. Transf. 11.5.)

18. Draw the first two steps of this synthesis. (Check your work: See Synthetic Transformation 13.4d.)

$HC \equiv CH$

ethyne (or acetylene)

starting material



acetone

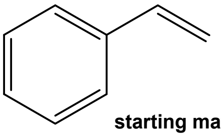
19. $HC \equiv C—CH_3$ is a precursor of acetone. This means it can be made into acetone in one synthetic step. Draw the third (and final) step in this synthesis. (Check your work: See Synth. Transf. 11.3)

Synthesis Tip 2: Know Your Synthetic Transformations!!

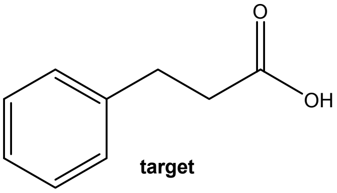
Hopefully this activity has convinced you that even a three-step synthesis problem will be impossible if you do not memorize every synthetic transformation we have encountered. If you have not already done so, make a set of three to four note cards for *each* synthetic transformation using the guidelines set out in the Exercises section of ChemActivity 8.

20. Look at Memorization Task 13.3 and find all three types of carbon nucleophiles on Table 13.2.
    a. In the next section we will learn about the nucleophile R_3C^{-}, so, for now, ignore this nucleophile. List the other two carbon nucleophiles from Table 13.2 (in Mem. Task 13.3).
    b. In the next question, how many carbons need to be added in going from starting material to target?

21. Parts a and b of this question ask you to use retrosynthesis to solve the synthesis problem in two different ways..
    a. Solve it using the one-carbon nucleophile in Table 13.2 (*Hint*: See Synthetic Transformation 11.6 if you are stuck thinking of a precursor for a carboxylic acid group, CO_2H.).

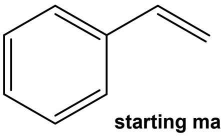


starting material

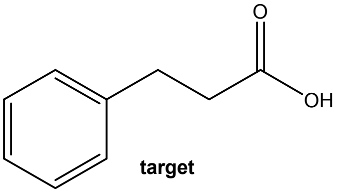


target

    b. Now solve it using the other carbon nucleophile from Table 13.2 ($RC\equiv C^{-}$). *Hint*: See Synthetic Transformation 10.11 if you are stuck.



starting material



target

PART B: LITHIUM AND GRIGNARD REAGENTS

(What are the special conditions required for preparation and use of Li and Mg organometallics?)

Model 4: Lithium Reagents and Grignard Reagents

We have learned so far in this course that R_3C^- is very high in potential energy. It turns out that carbon does not form useful salts with the usual **counterions** (e.g., $NaCH_3$ and KCH_3 have no synthetic utility).

However, it does form useful salt-like reagents with some metals, including lithium and magnesium. These are examples of **organometallic reagents**, so called because they have a metal-carbon bond.

Lithium and Grignard reagents are prepared from alkyl halides by a poorly understood mechanism. Though there are differences between them, we will assume lithium and Grignard reagents are interchangeable, each behaving like a carbon anion, that is, an **excellent nucleophile** and an **extremely strong base** (releases about **35 p*K*** units of energy upon forming a new bond to an acidic H).

"Grignard Reagents" are named for French chemist Victor Grignard (1871-1935), pronounced "green-yard."

Synthetic Transformation 16.1: Lithium or Grignard reagent from an alkyl halide

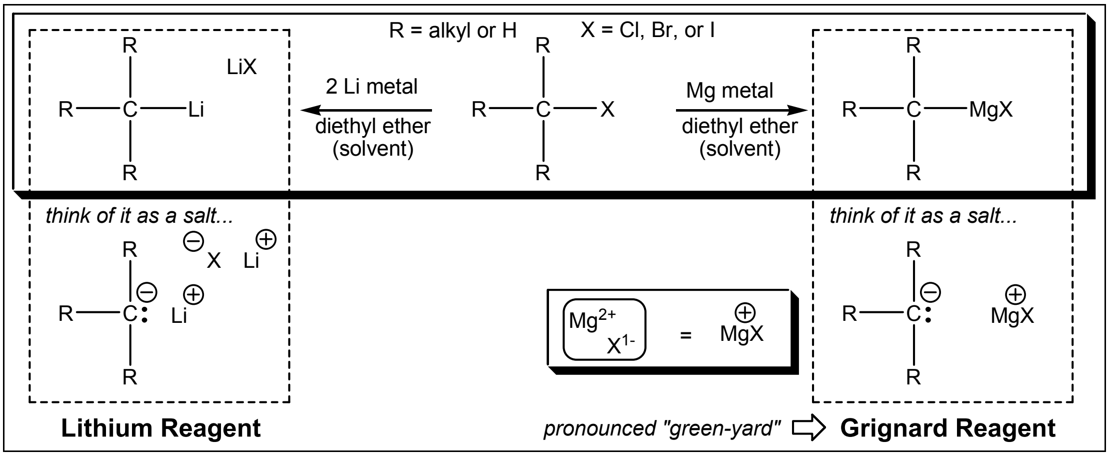


Figure 16.4: Preparation of lithium and Grignard reagents

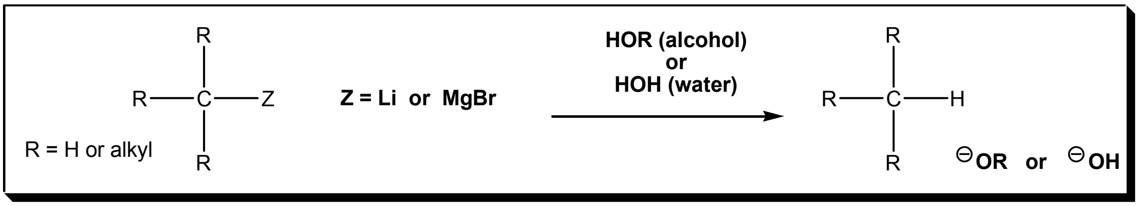
Critical Thinking Questions

22. Consider the lithium and Grignard reagents in Figure 16.4.
    a. (E) Given its position on the periodic table, what is the likely positive charge on a Li ion?
    b. (E) Given its position on the periodic table, what is the likely positive charge on a Mg ion?
    c. (E) What is the charge on a Br ion?
    d. (E) What is the total charge on a combined [MgBr] ion?
    e. (E) Is your answer to the previous question consistent with the fact that a Li or [MgBr] ion can act like a counterion for a carbon with a -1 charge?

Memorization Task16.2: Think of lithium and Grignard reagents as salts.

You will see these reagents drawn as having a covalent bond between C and Li or MgBr (as in the top representations in Figure 16.4), but they behave as if there is a –1 charge on carbon and a +1 charge on Li or MgBr. It may help to draw the reagents as salts (as in the bottom representations in Figure 16.4).

Synthetic Transformation 16.2: Reaction of a lithium or Grignard reagent as a base

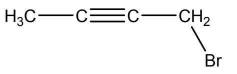


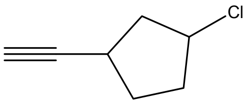
Memorization Task 16.3: Use only unfunctionalized R groups to make R—Li or R—MgX.

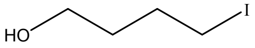
Because of their extreme basicity, lithium and Grignard reagents CANNOT be made from an alkyl halide (R—X) containing an H with a pK_a less than 35. For the same reason, water interferes with the preparation and use of these reagents. Flame-dried glassware is often used for these reactions.

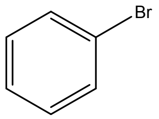
Critical Thinking Questions

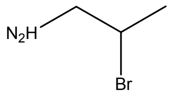
23. Cross out the alkyl halides that CANNOT be used to make a lithium or Grignard reagent.







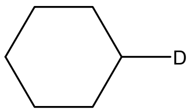




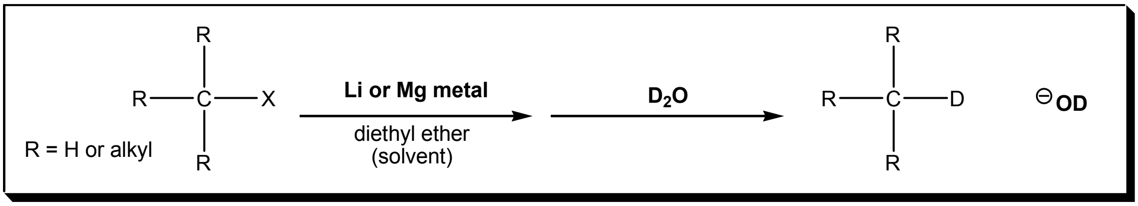
24. Draw the Grignard reagent formed by mixing bromocyclohexane with magnesium metal. (As in Figure 16.4, show it two different ways, with a covalent bond between C and MgBr and as a salt.)

a. Use curved arrows to show an acid-base reaction between water and **each representation** of the Grignard you drew above.

b. What reagent could you mix with the Grignard above to produce monodeuterocyclohexane? → →



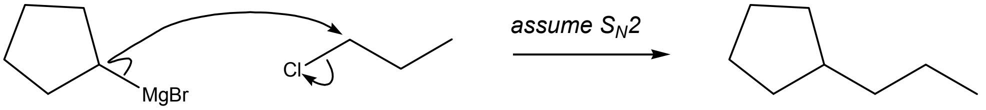
Synthetic Transformation 16.3: Replacement of a halogen with a deuterium



Model 5: Carbonyl (C=O) Compounds, alternates to R—X

In Part A we learned that an alkyl halide (e.g., R—X) serves very well as an electrophile in reaction with the nucleophile $HC{\equiv}C^{-}$. Though lithium and Grignard reagents are good nucleophiles, for reasons we will not discuss they do not give good product yields in reactions with **alkyl halide electrophiles**.

Memorization Task 16.4: Lithium and Grignard reagents do not react well with R—X



low yield of this product

Note: Though the actual mechanisms are more complex, it is useful to assume that lithium and Grignard reagents react the same way as other strong-base nucleophiles, that is, via S_N2 *(as shown above).*

Term Introduction: Carbonyl Compound = molecule containing a carbonyl (C=O) group

A functional group of the form $Z_2C{=}O$ (containing a **carbonyl group**) is called a **carbonyl compound**. So far we have encountered aldehydes (Z_i = H, Z_{ii} = alkyl), ketones (Z_i and Z_{ii} = alkyl), and carboxylic acids (Z_i = alkyl, Z_{ii} = OH). Later we will encounter several other common variations.

Due to the polarization of the C=O bond, the C of a carbonyl group is usually a very good electrophile.

Memorization Task 16.5: Lithium and Grignard reagents react well with C=O electrophiles

Synthesis Tip 3: There are two main types of carbon electrophiles, $Z_2C{=}O$ and $R_3C{—}X$

(usually) The synthetic equivalent for a synthon with a $C^{\delta+}$ will be a carbonyl compound or alkyl halide.

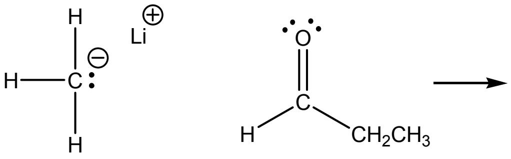
Critical Thinking Questions

25. Draw a carbonyl compound of the form $R_2C{=}O$ in which one R = H and the other R = CH_2CH_3.

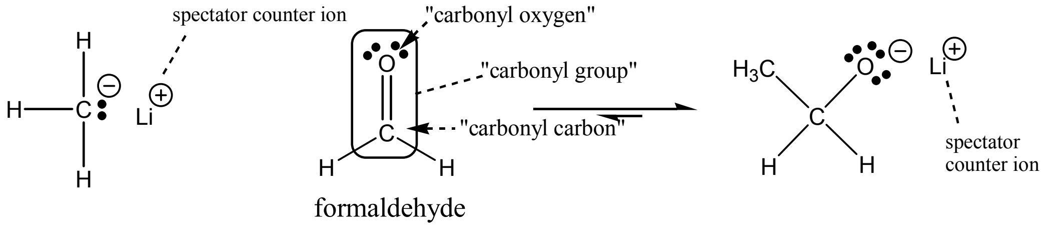
    a. Add a δ+ and a δ– to this molecule to show the polarization of the carbonyl (C=O) bond.

    b. What is the name of this type of functional group (a C=O attached to one H and one alkyl)?

26. Use curved arrows to show how the nucleophile CH_3—Li (shown below as a salt) might react with a carbonyl compound, and draw the resulting products.



Model 6: Nucleophilic Addition to a Carbonyl (C=O)



Note: The product is sometimes shown with a covalent bond between O and Li.

Critical Thinking Questions

27. Add curved arrows to Model 6 that account for the product shown, then check your work in the CTQ at the bottom of the previous page.

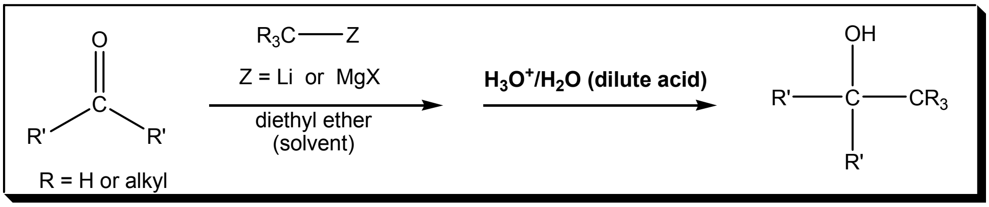
28. The **alkoxide** (RO$^-$) product in Model 6 is itself a strong base and a good nucleophile.

    a. Draw the product that results if the product shown in Model 6 is neutralized with dilute acid (H_3O^+/H_2O).

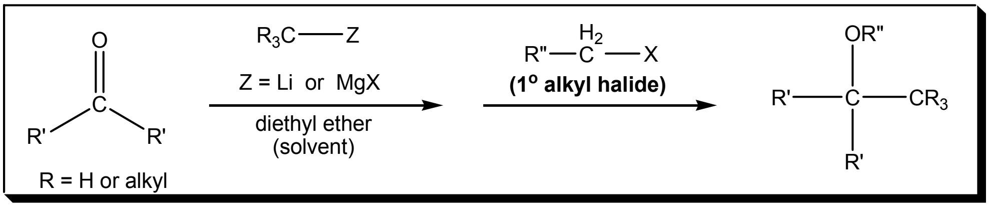
    b. Draw the product that results if the product shown in Model 6 is treated with the alkyl halide CH_3CH_2—I (instead of dilute acid).

Synthetic Transformations 16.4 and 16.5: Alcohol or ether from an aldehyde or ketone

16.4



16.5



29. Draw the most likely product of the following sequence of reactions starting with cyclohexane.

$$\text{cyclohexane} \xrightarrow[\text{one molar equiv. Cl}]{Cl_2\ \ h\nu} \xrightarrow[\text{diethyl ether (solvent)}]{Li^0} \xrightarrow{O{=}C(CH_3)_2\ \ \text{(acetone)}} \xrightarrow{CH_3CH_2CH_2Br}$$

Model 7: Reduction of Aldehydes or Ketones to Alcohols

Many nucleophiles will react with a carbonyl carbon. We will explore more possibilities in future activities. Here we discuss one small but very important nucleophile, **hydride anion (H^-)**.

As with carbon, the sodium and potassium salts of hydrogen (NaH and KH) are not nearly as useful as other reagents that deliver an H^-. The most common are $LiAlH_4$ and $NaBH_4$

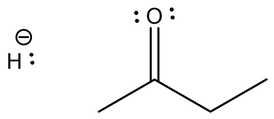
Memorization Task 16.5: $LiAlH_4$ and $NaBH_4$ react as if they were a hydride anion (H^-)

$LiAlH_4$ (lithium aluminum hydride) = strong H^- delivery reagent (reacts with any carbonyl)

$NaBH_4$ (sodium borohydride) = milder H^- delivery reagent (reacts with only aldehydes and ketones)

Critical Thinking Questions

30. Use curved arrows to show the mechanism, and draw the products of the most likely reaction between a hydride anion (H^-) and the ketone below.



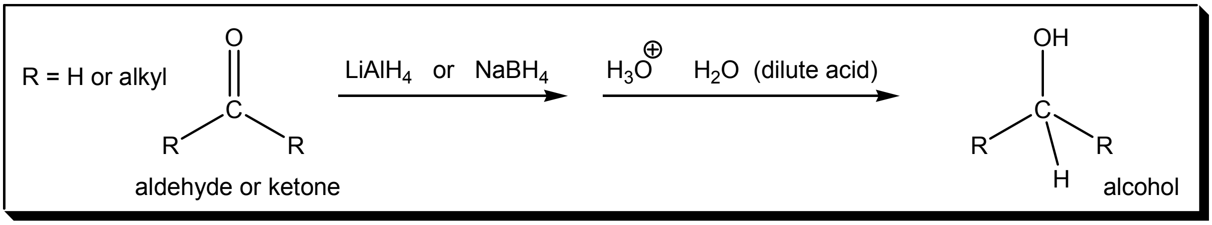
31. (Check your work.) The product of a reaction in the previous question should be an alkoxide (RO^-), a strong base and a good nucleophile.

    a. Draw the result if the product from the reaction in the previous question is treated with dilute acid (H_3O^+/H_2O).

    b. Is your answer to a consistent with Synth. Transf. 16.6?

    c. Draw the product that results if the product from the reaction in the previous question is treated with the alkyl halide $CH_3CH_2CH_2$—I (instead of dilute acid).

Synthetic Transformation 16.6: Reduction of an aldehyde or ketone to an alcohol



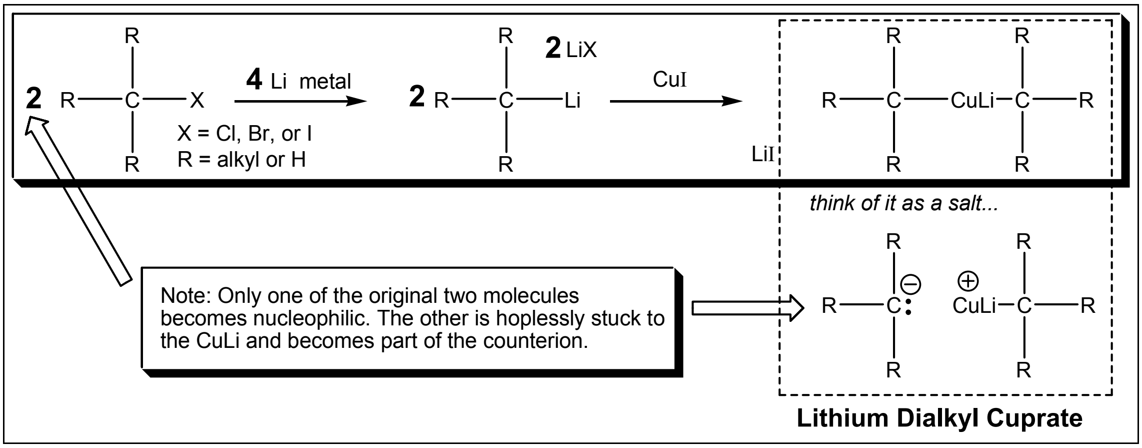
PART C: LITHIUM DIALKYL CUPRATE REAGENTS

(How do lithium dialkyl cuprates differ from Grignard and ordinary lithium reagents?)

Model 8: An Alternative to Lithium and Grignard Reagents

Like Grignards and ordinary lithium reagents, **lithium dialkyl cuprate (LiR_2Cu) reagents** behave as if they are a salt consisting of an anionic carbon nucleophile (R^-) and a positive counterion ($[CuLiR]^+$).

Synthetic Transformation 16.7: Lithium dialkyl cuprate reagent from an alkyl halide



Note: Only one of the original two molecules becomes nucleophilic. The other is hoplessly stuck to the CuLi and becomes part of the counterion.

LiR_2Cu reagents were developed as an alternative to existing organometallic reagents. They are softer and milder than ordinary lithium or Grignard reagents and work in situations where the others typically fail.

Their development took place in the past 30 years, spearheaded by four still-active giants of organic chemistry: E. J. Corey of Harvard, Gary H. Posner of Johns Hopkins, Herbert O. House of Georgia Tech, and George M. Whitesides of MIT.

Memorization Task 16.7: Lithium dialkyl cuprates react best with alkyl halide electrophiles.

In fact, they have the opposite electrophile preferences from lithium and Grignard reagents. Lithium dialkyl cuprates DO NOT react with aldehydes and ketones, but react very well with alkyl halides.

Critical Thinking Questions

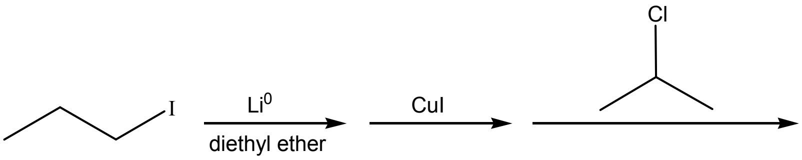
32. You are a graduate student who has spent a year making an elaborate chiral alkyl halide (*R—Br). Even considering your meager stipend, the cost of making this alkyl bromide is $20,000 per gram.
    a. (E) How many molecules of *R—Br are needed to create one molecule of the lithium dialkyl cuprate nucleophile (*R^-) based on your chiral alkyl bromide?
    b. (E) Construct an explanation for why chemists avoid using LiR_2Cu reagents when the R group is very costly.

33. Cu(I) makes a +1 ion, and Cu(II) makes a +2 ion. What type of copper is in the counterion of the nucleophilic part of a lithium dialkyl cuprate reagent $[CuLiR]^+$? **Cu(I)** or **Cu(II)**? (circle one)

34. Draw the lithium dialkyl cuprate reagent formed by mixing 2-chlorobutane with lithium metal, followed by treatment with copper iodide. As in Model 8, show it two different ways: i) with covalent bonds between carbon and metal, and ii) as a salt.

35. Lithium dialkyl cuprates react very well with one main type of carbon electrophile and poorly with the other type. Draw an example of a carbon electrophile that a LiR_2Cu reagent would react with well, and an example of a carbon electrophile that it will react with poorly (or not at all). (*Hint*: See Synthesis Tip 3 in Model 5 of this ChemActivity.)

36. Draw the product of the following reaction sequence.

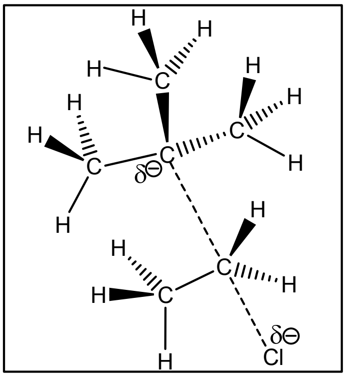


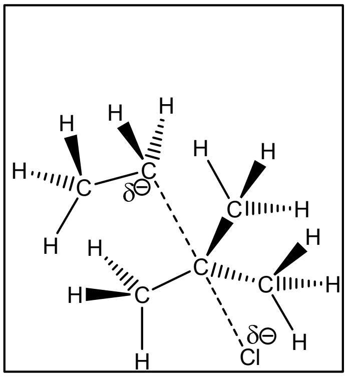
Synthesis Tip 4: Keep track of carbons. Always count starting material C's and target C's.

37. Use **Synthesis Tip 4** to check your work in the previous question.

38. Find the nucleophilic carbon and the electrophilic carbon on each S_N2 transition state (ts‡) at right, and label each of these 1° or 3°, as appropriate.

39. Label one ts‡ "**3° Nuc/1° Elect**" and the other "**1° Nuc/3° Elect**"





40. S_N2 reactions are limited by crowding in the transition state around the electrophilic carbon. In fact, we learned in CA 13 that S_N2 reactions do not occur at 3° electrophilic carbons. Cross out the ts‡ above that is very unfavorable due to **steric effects**.

41. Construct an explanation for the statements in Memorization Task 16.8.

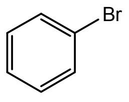
Memorization Task 16.8: A bulky (3° or 2°) nucleophile is better than a bulky electrophile

Steric bulk (crowding around the electrophilic carbon) always slows down an S_N2 (or S_N2-like) reaction. But if one reagent must be bulky (e.g., 3°) it should be the nucleophile, not the electrophile.

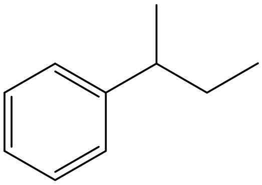
In fact, **LiR_2Cu reagents react with 0°, 1°, and 2° alkyl halides, but NOT with 3° alkyl halides**.

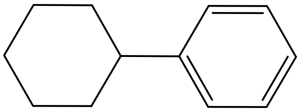
42. The product (2-methylpentane) of the synthesis near the top of the page is better made using a different synthesis. Show a better synthesis of 2-methylpentane using these same two alkyl halides.

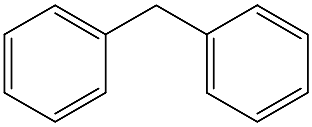
43. Each of the following targets was synthesized by mixing a lithium dialkyl cuprate made from bromobenzene with another alkyl halide. Below each target, draw this other alkyl halide. Use retrosynthesis: Start by “cutting” the new bond in the target with a squiggle as in Model 3.



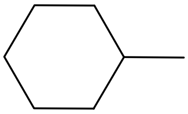
bromobenzene

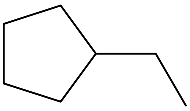


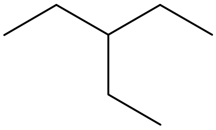


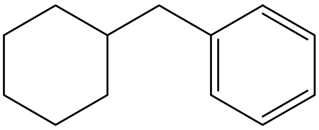


44. Use retrosynthesis to determine a lithium dialkyl cuprate/alkyl halide pair that could be combined to make each of the following targets. There are multiple acceptable answers for each one. (In the homework exercises you are asked to find all possibilities for each.)

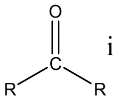




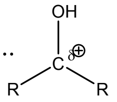




Synthesis Tip 5:



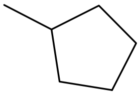
is a synthetic equivalent of the synthon...



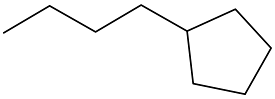
R = H or alkyl

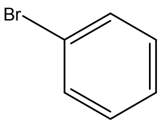
45. Use retrosynthesis to design a synthesis of each target using the starting material and any other reagents containing **three or fewer carbons**.

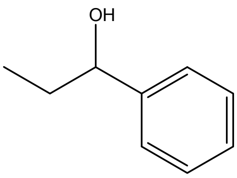
starting material



target







Model 9: Functional Group Approach

One way to organize a textbook or course is by **functional group**. For example, you can find a chapter in most other textbooks called “Alcohols” that has sections on naming alcohols, making alcohols, and reactions of alcohols.

The chapters in this workbook are instead organized around the main reaction types: electrophilic addition, nucleophilic substitution, elimination, nucleophilic addition, (and still to come) addition-elimination, and nucleophilic and electrophilic aromatic substitution.

However, now that we are beginning organic synthesis it is important that you know the names and characteristics of the main organic functional groups. More and more we will be asking questions about functional group transformations. (What reagent will transform an alcohol to an alkyl bromide?) Mechanisms for many reactions will still be important, but the emphasis is shifting toward synthesis.

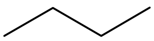
Critical Thinking Questions

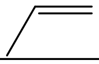
46. Below are examples of molecules containing various functional groups.

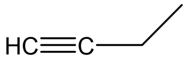
    a. Match the name of the functional group with the appropriate molecule. Choose from: **Amine, Alcohol, Aldehyde, Alkane, Alkene, Alkyl Halide, Alkyne, Carboxylic Acid, Epoxide, Ether, Ketone, Nitrile (cyano), Nitro, Phenyl Group (benzene ring) and Thiol.**

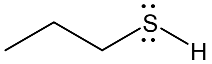
    b. Next to the carboxylic acid, draw its conjugate base (a **carboxylate ion**).

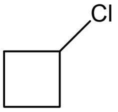
    c. Next to the amine, draw its conjugate acid (an **ammonium ion**).

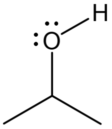


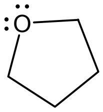


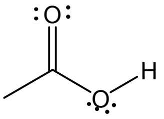


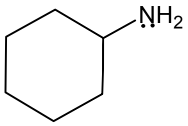


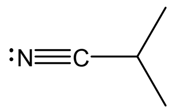


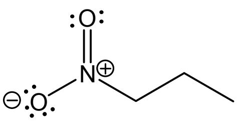


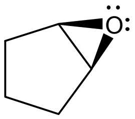


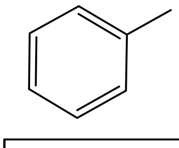


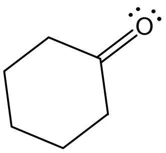


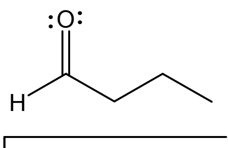










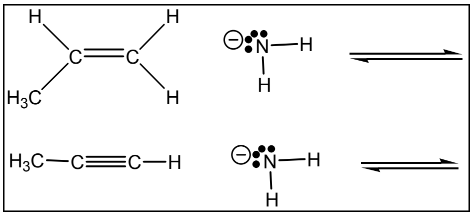


Memorization Task 16.9: Be able to recognize and name each functional group type above.

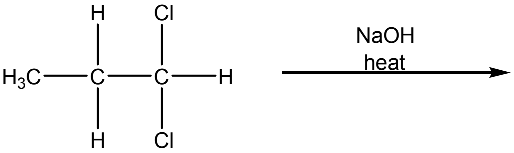
Exercises for Part A

1. Draw at least two precursors of ….
   a. an alkene
   b. an alkyl bromide
   c. an alcohol
   d. a diol

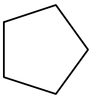
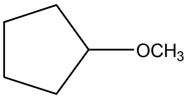
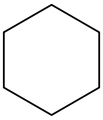
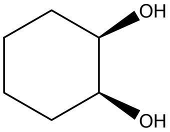
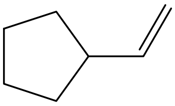
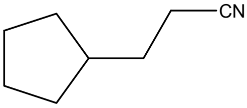
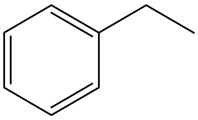
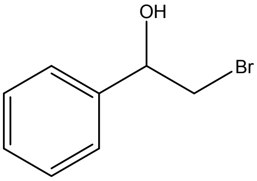
2. Consider the acid-base reactions at right.
   a. Use curved arrows to show each reaction.
   b. Draw the products of each reaction.
   c. For each reaction, estimate ΔH_{rxn} using p*Ka* values
   d. Which reaction is downhill (favorable), and which reaction is uphill (unfavorable)?
   e. Explain why the methyl H's were not removed in either case.



3. Heating a **geminal dihalide** in base gives an alkyne. Show the mechanism and products of the following reaction.



4. Use retrosynthesis to design a synthesis of each target using the starting material and any reagents containing one carbon or less.

Starting Material	Target
	
	
	
	

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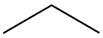
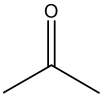
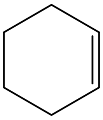
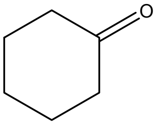
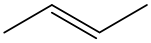
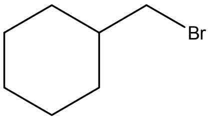
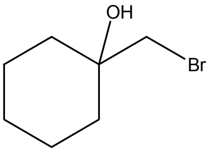
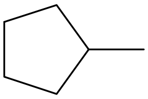
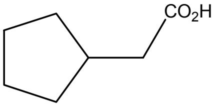
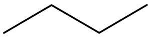
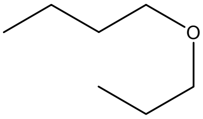
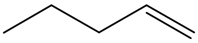
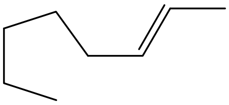
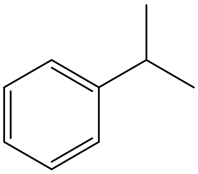
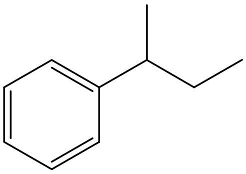
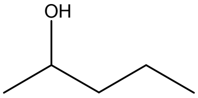
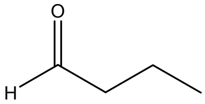
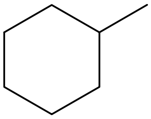
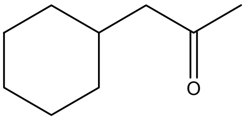
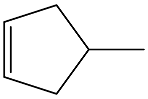
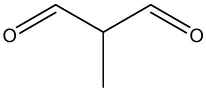
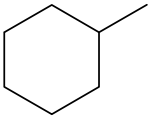
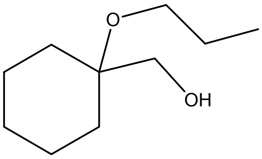
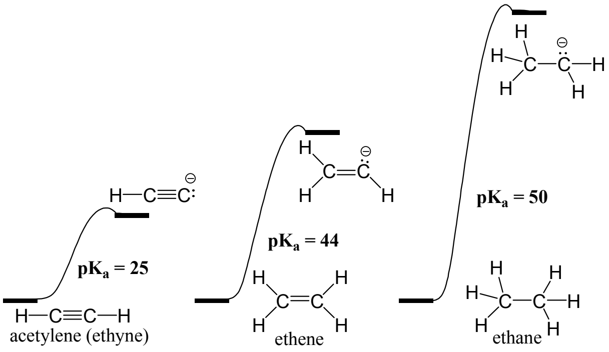
	
	
$HC\equiv CH$	
	

5. Use retrosynthesis to design a synthesis of each target using the starting material and any reagents containing three carbons or less.

Starting Material	**Target**
	
	
	
	

Starting Material	**Target**
	
	
	
	



6. Explain why an electron pair in an *sp* hybrid orbital is lower in potential energy than an electron pair in an sp^2 hybrid orbital.

7. Explain why ethyne is more acidic than ethene or ethane.

8. Construct an explanation for why the C—H bond in ethyne is shorter than the C—H bond in ethene or ethane (even though it is easier to break with a base).

9. True or False: It is easier to reduce the first π bond of a triple bond than the second π bond. Cite evidence from one or more Synthetic Transformations to support your choice.

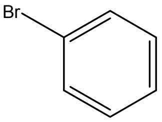
10. Read the assigned pages in the text, and do the assigned problems.

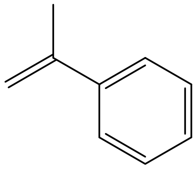
Exercises for Part B

11. Draw a precursor of ….
    a. an aldehyde (RHC=O)
    b. a ketone ($R_2C=O$)
    c. a carboxylic acid (RCO_2H)
    d. a bromohydrin (Br and OH on adjacent carbons)

12. Show a synthesis of 2-deutero-2-methylpropane from 2-methylpropane.

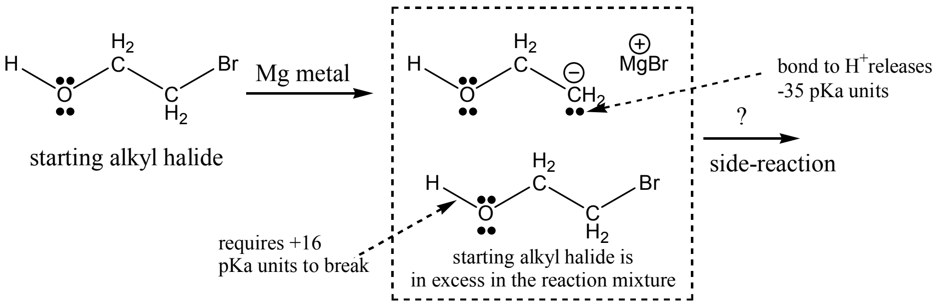
13. Use retrosynthesis to design a synthesis of the following molecule from bromobenzene.





14. Lithium and Grignard reagents are extremely strong bases. Upon making a bond to H^+ they release a large amount of energy (you may assume about 50 pKa units, but actually the value is closer to 35–40 p*Ka* units of energy). Recall that the p*Ka* of an alcohol is about 16. (Requires 16 p*Ka* units of energy to remove an H^+.)

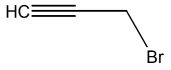
    a. In the reaction below, the moment a molecule of Grignard reagent is formed, it immediately undergoes an acid-base reaction with a second molecule of starting material. Use curved arrows to show this unwanted side reaction, and draw the products.

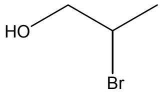


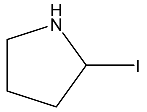
    b. Construct an explanation for why preparation of lithium and Grignard reagents **cannot** be performed with an alkyl halide containing an H with a $pK_a < 35$.

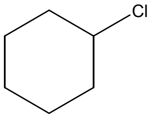
15. How does the mechanism of nucleophilic addition differ from nucleophilic substitution? Do the names reflect these differences?

16. Which of the following are unacceptable alkyl halides for making a Grignard or lithium reagent?





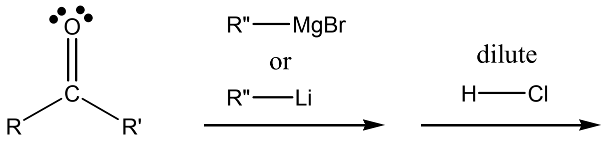




Rule of Thumb: In general, an alkyl halide with any other functional group is not suitable for making a Grignard or lithium reagent.

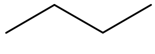
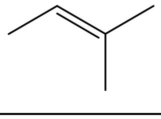
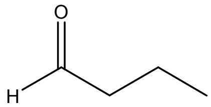
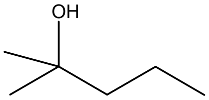
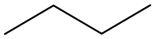
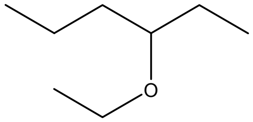
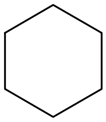
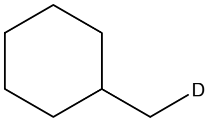
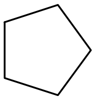
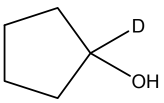
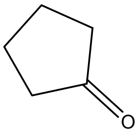
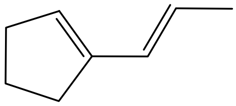
17. For each unacceptable alkyl halide in the previous question, show the side reaction that would occur if each were treated with Li or Mg.

18. Draw the alcohol product that results when an aldehyde or ketone is…
    a. treated with a Grignard or Lithium reagent (strong nucleophile)
    b. then neutralized with dilute acid



(aldehyde when R or R' = H)

19. Design a synthesis of each target using the starting material and any reagents containing three carbons or less.

Starting Material	Target	Starting Material	Target
			
			
			

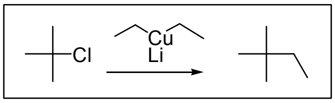
20. Read the assigned pages in the text, and do the assigned problems.

Exercises for Part C

21. Recall that S_N2 reactions give only a reasonable yield of product when a methyl, primary, or unhindered secondary leaving group is involved. Even though lithium dialkyl cuprate reagents undergo a mechanism more complicated than S_N2, you can usually assume that their mechanism of reaction is very similar to an S_N2.

    a. Explain why each of the following reactions will not give an optimum yield of the product (*Hint*: See Memorization Task 16.8.).

    b. Under each reaction draw a pair of reagents that would give the product in a better yield.

i)


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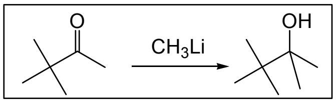

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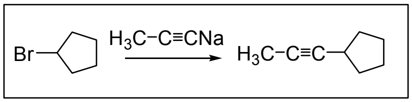
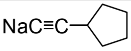
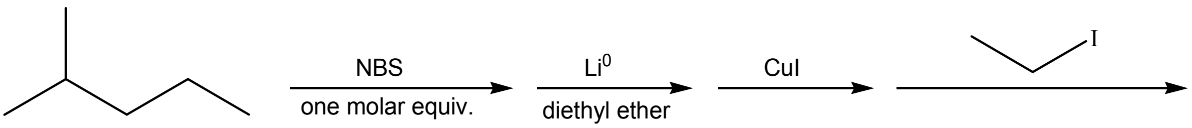


Hint: Use


as your nucleophile.

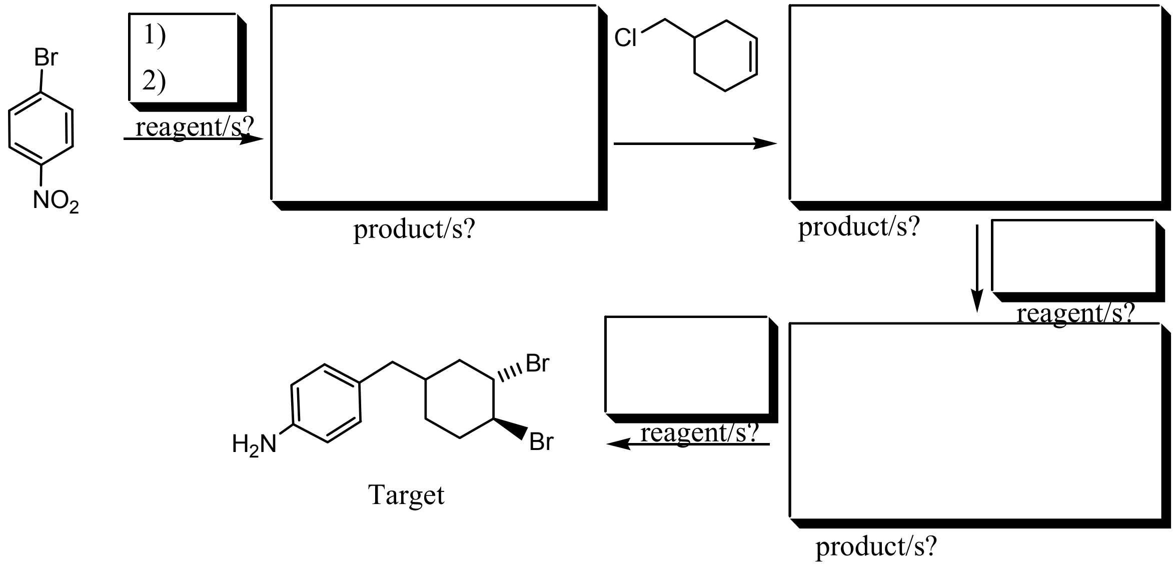
22. Draw the most likely product of the following reaction sequence.



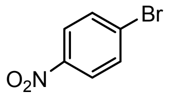
Synthetic Transformation 16.8: Reduction of a nitro group to an amine

$$R{-}NO_2 \xrightarrow{\substack{\text{zinc metal/mercury metal amalgam = "Zn(Hg)"} \\ \text{HCl}}} R{-}NH_2$$

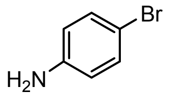
23. Fill in missing reagents and products in the following multi-step synthesis.



24. Explain why the synthesis in the previous question would not work if you started with 4-bromoaniline instead of 4-bromonitrobenzene. Draw the side reaction that completely consumes the carbon anion before it can be used in the desired second step.



4-bromonitrobenzene

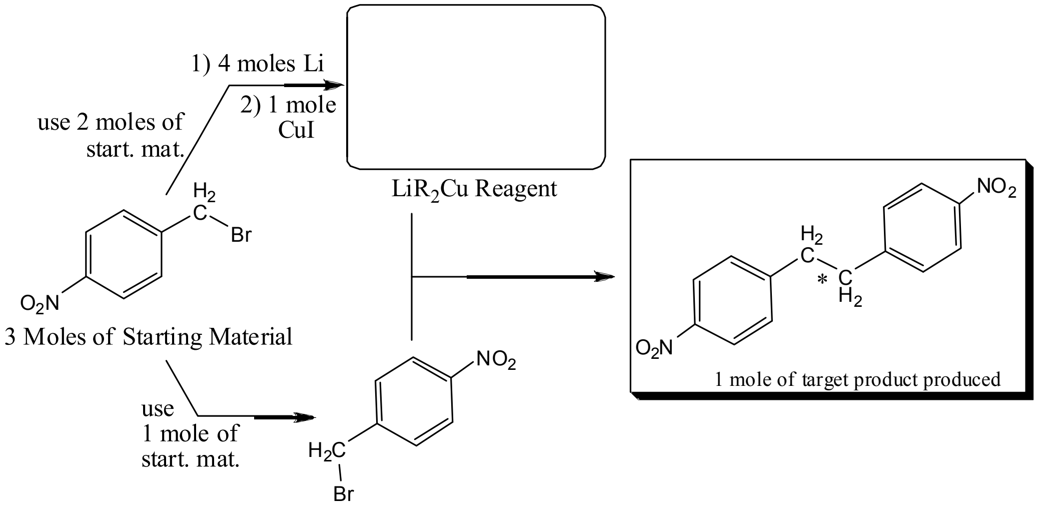


4-bromoaniline

25. Synthesis of one mole of the following target molecule can be accomplished using three moles of the starting material shown below.

    a. Two moles of the starting material are used to prepare a LiR_2Cu reagent. Draw this reagent in the box provided, showing a full −1 charge on C.

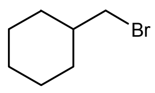
    b. This LiR_2Cu reagent is added back to the rest of the starting material. Assume an S_N2 mechanism, and use curved arrows to show how the final step might occur.


1) 4 moles Li
2) 1 mole CuI
use 2 moles of start. mat.
H_2
C
Br
O_2N
3 Moles of Starting Material
LiR₂Cu Reagent
use 1 mole of start. mat.
NO_2
H_2C
Br
NO_2
H_2
C
*
C
H_2
O_2N
1 mole of target product produced

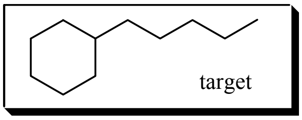
26. Design a synthesis of the target (pentylcyclohexane) from bromomethylcyclohexane using each method described below.

    a. using any alkyne

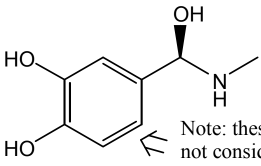
    b. using any lithium dialkyl cuprate reagent.



starting material

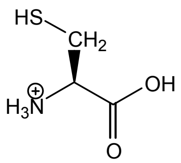


27. Circle and name each functional group in the following multi-functional group molecules.



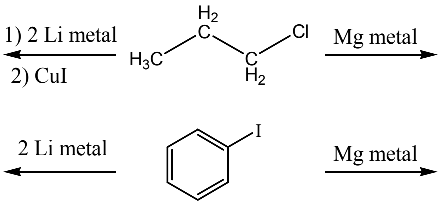
Note: these three π bonds are not considered alkenes because they are resonance stabilized-and so do not react like alkenes

Adrenaline

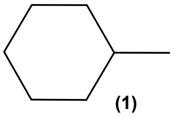


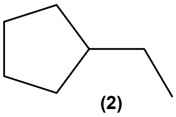
Cysteine (an amino acid)

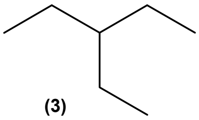
28. Alkyl bromides are the most common starting materials for preparing Grignard, lithium, and lithium dialkyl cuprate reagents, but Cl and I also work. Draw the products of each of the following reactions, and **show the products as ions** to emphasize the polarization of the carbon-metal bond.

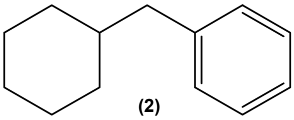


29. Use retrosynthesis to determine a lithium dialkyl cuprate/alkyl halide pair that could be used to make each of the following targets. There are multiple acceptable answers for each target except methylcyclohexane. The number of possibilities is given in parentheses below each target. This number does not include inferior routes (e.g., 1° nucleophile with a 2° electrophile when the opposite is possible.)

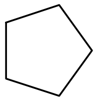
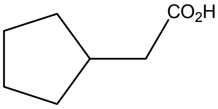
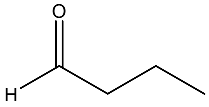
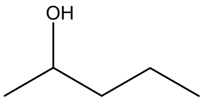
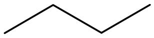
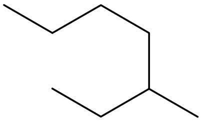
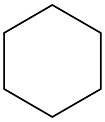
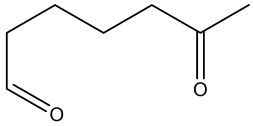
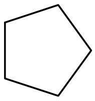
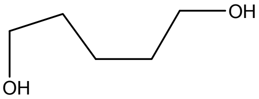
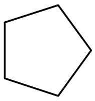
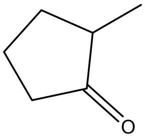
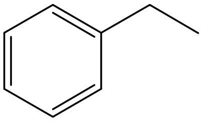
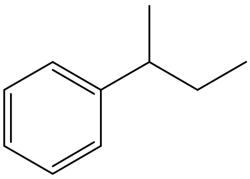
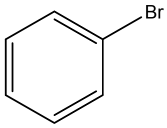
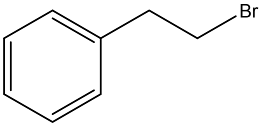

(1)


(2)


(3)


(2)

30. Design a synthesis of each target using the starting material and any reagents containing two carbons or less.

Starting Material	Target	Starting Material	Target
			
			
			
			

31. Read the assigned pages in the text, and do the assigned problems.

The Big Picture

Most organic chemistry students find synthesis to be the most challenging aspect of the course, but it is potentially the most fun and creative. Synthesis problems are this course's best approximation of the open-ended problems that dominate research and medicine. Often the hardest part of a synthesis problem is getting started and developing a plan. The Common Points of Confusion section outlines some study strategies that will help you do this, making many synthesis problems trivial and the others an exciting challenge.

Synthesis is going to appear on every exam and in every chapter of this book and is the work of the majority of organic chemists, those called synthetic organic chemists.

Common Points of Confusion

As with every topic in this course, the situation is not nearly as bad as you think. Do not let the reputation of this course or your anxiety get in the way of enjoying one of the most creative and potentially fun challenges you will encounter in all of science: organic synthesis.

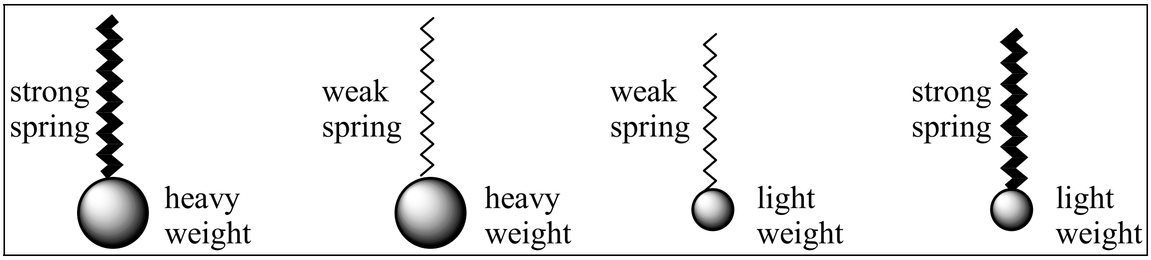
- **Memorize all the Synthetic Transformations** using the four-note-card strategy outlined in the Exercises of ChemActivity 8. You must know these forward and backward.
- Do synthesis problems working both from the starting material forward and, using retrosynthesis, from the target backwards.
- Don't waste time staring at a blank page. Keep your pencil moving and your brain will follow. Start each synthesis by listing the possible first steps forward from the starting material AND the possible last steps, thinking backwards (retrosynthetically) from the target.
- Many two-to-four-step synthesis problems can be solved in the forward direction without using retrosynthesis, but retrosynthesis is an invaluable tool for developing a plan for solving more complicated syntheses. If you do not understand the point or methods of retrosynthesis, study Part A of this activity, and discuss it with a person who seems to like synthesis.
- Chess masters study games played by other masters to learn common sequences of moves. Study the solutions to synthesis problems to build your repertoire of common sequences of transformations.
- Make up your own synthesis problems, and share them with your study partner.

ChemActivity L1: Infrared (IR) Spectroscopy

(What can an IR spectrum tell you about the structure of a molecule?)

Demonstration: Weights Bouncing on Springs

Consider a weight suspended from a spring (or rubber band) that is dropped and allowed to bounce. Before seeing a demonstration, **predict** with your group which case below will have the **fastest frequency** (number of bounces per unit time) and which will have the **slowest frequency**.



Critical Thinking Questions

1. Circle each of the following statements that fits with what you observed in the demonstration. **Cross out** each one that **does not fit** with what you observed.

   (1) The stronger the spring, the higher (faster) the frequency of bouncing.

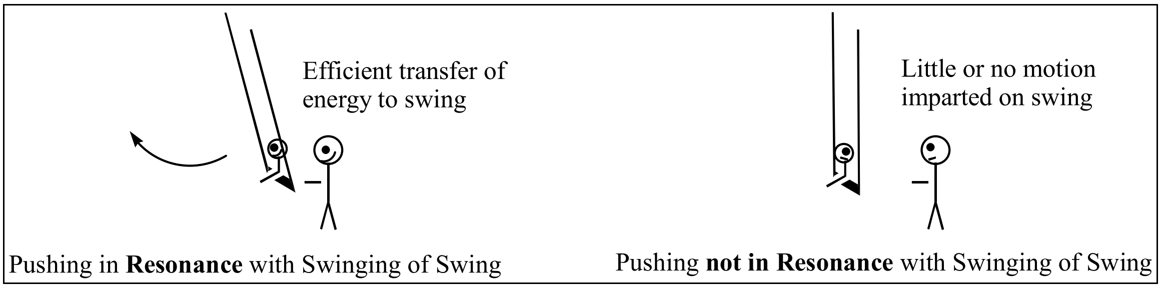
   (2) The weaker the spring, the higher (faster) the frequency of bouncing.

   (3) The heavier the weight, the higher (faster) the frequency of bouncing.

   (4) The lighter the weight, the higher (faster) the frequency of bouncing.

Model 1: Resonant Frequency

Consider a parent pushing a child on a swing. If the parent pushes at the exact right intervals, energy will be absorbed by the swinging child, and she will go higher. If the parent pushes at the wrong moments, the swinging child will not absorb energy from the parent, and the swing will not go higher.


Efficient transfer of energy to swing
Little or no motion imparted on swing

Pushing in **Resonance** with Swinging of Swing

Pushing **not in Resonance** with Swinging of Swing

frequency = **cycles per unit time (1 cycle/second = 1 Hertz = 1 Hz = 1 s^{-1})**. If the frequency of pushing matches the frequency of swinging, then the two are in **resonance** with each other.

Critical Thinking Questions

2. Frequency can be a measure of any repeating phenomenon. What other phenomena around us are measured in frequency?

Model 2: Wavelength and Energy

Many phenomena around us can be measured in frequency (Hz), including ocean waves and **light waves**.

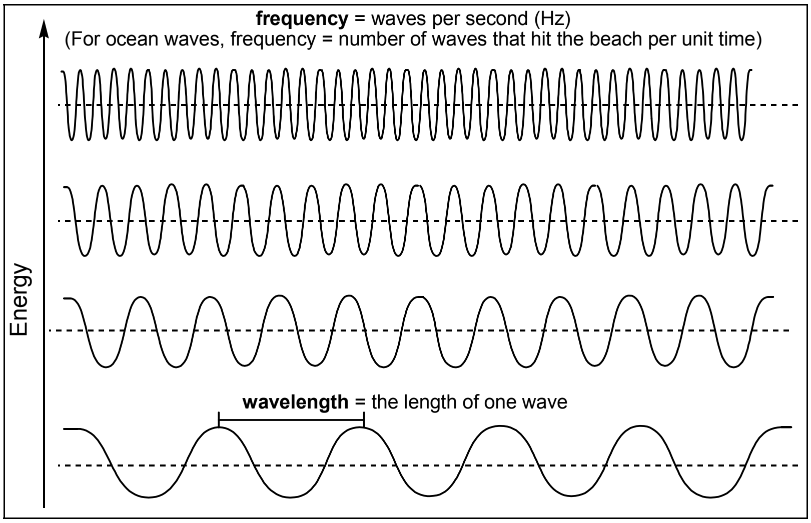

frequency = waves per second (Hz)
(For ocean waves, frequency = number of waves that hit the beach per unit time)
Energy
wavelength = the length of one wave

Figure L1.1: Light (or ocean) waves

Critical Thinking Questions

3. Label the wave with the **shortest wavelength** and the wave with the **longest wavelength**.

4. You can think of frequency in Hz (cycles) as the number of wave peaks that pass a given point in a second. Assume the cartoon waves above are moving at the same speed, and label the wave with the **highest frequency** and the wave with the **lowest frequency**.

5. Which has more energy, a **high-** or **low-**frequency wave (circle one).

Table L1.1: Electromagnetic Spectrum

Type of Light	Frequency (in Hz)	Wavelength (λ)	Effect	Energy
X-ray	$10^{17} – 10^{19}$	λ = 0.1 - 10 nm	causes cancer	**extremely high**
Ultra-violet (UV)	around 10^{15}	λ = 200 - 400 nm	causes sun burn	**high**
Visible	around $10^{14.5}$	λ = 400 - 800 nm	energy for plants	**moderate**
Infrared (IR)	around 10^{13}	λ = 1000 – 100,000 nm	transfers heat	**low**
Radio Waves	$1 – 10^{9}$	λ = 0.2 - 20 m (10^{9} nm)	relatively safe	**very low**

Critical Thinking Questions

6. Are your answers to the previous three questions consistent with the **electromagnetic spectrum** data in Table L1.1 and the fact that wavelength is **inversely proportional** to frequency and energy?

Model 3: Bonds Are Like Springs

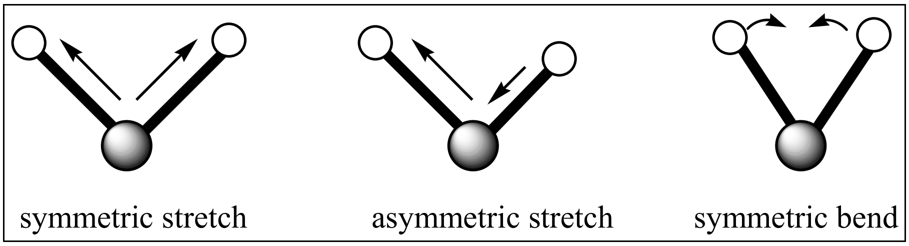


Figure L1.2: Some of the Stretching and Bending Motions of Water

Bonds stretch, bend, and wag as if they were balls attached by springs. A light wave of the correct frequency will be **in resonance with** a bond motion and transfer its energy to this motion, like the parent pushing the swinging child. We say the light is **absorbed** by the molecule.

Microwave light (which is of lower frequency than IR) is absorbed very efficiently by water and excites what are called the rotational states of water. This is how your microwave oven adds energy to (heats) water.

Critical Thinking Questions

7. Pretend that your hands are the H atoms of water and your torso is the oxygen of water. Do the water molecule dance with your group, demonstrating the **symmetric stretch**, the **asymmetric stretch** and the **symmetric bend**.

8. Water molecules do all these at once (try that!), plus some other motions not shown. Each unique motion absorbs a unique frequency (ν) of light in the infrared range. Answer the following questions relating to the cartoon experiment below:

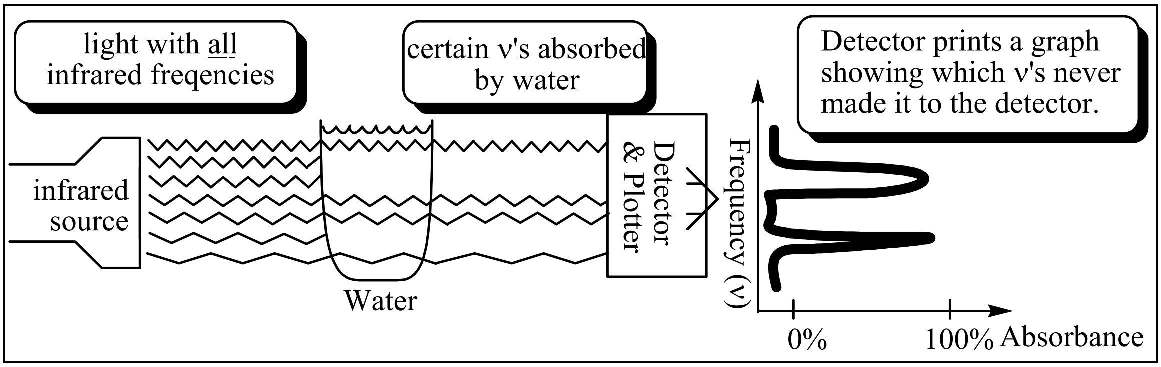

light with all infrared freqencies
certain ν's absorbed by water
Detector prints a graph showing which ν's never made it to the detector.
infrared source
Water
Detector & Plotter
Frequency (ν)
0%
100%
Absorbance

Figure L1.3: IR light absorbed by water

   a. What happened to the light that was **absorbed** by the water?

   b. Why are some frequencies (ν) of infrared light **transmitted** through the water?

9. In the diagram above, does a peak on the graph represent frequencies (ν) that were **absorbed** by the water or frequencies that were **transmitted** through the water?

10. Which of the following carbon-carbon bonds is stronger?

$H_2C{=}CH_2$	$HC{\equiv}CH$
Most carbon-carbon double bonds absorb light of ν = A	Most carbon-carbon triple bonds absorb light of ν = B

11. The Greek letter "nu" (ν) is used to represent **frequency.** Label light ν = A and light ν = B, above, with "**higher ν**" or "**lower ν**" based on the spring demonstration.

Model 4: Infrared Spectroscopy

Many bonds of interest to organic chemists are excited by (and absorb) light in the infrared (IR) region of the electromagnetic spectrum (frequencies near 10^{13} cycles per second).

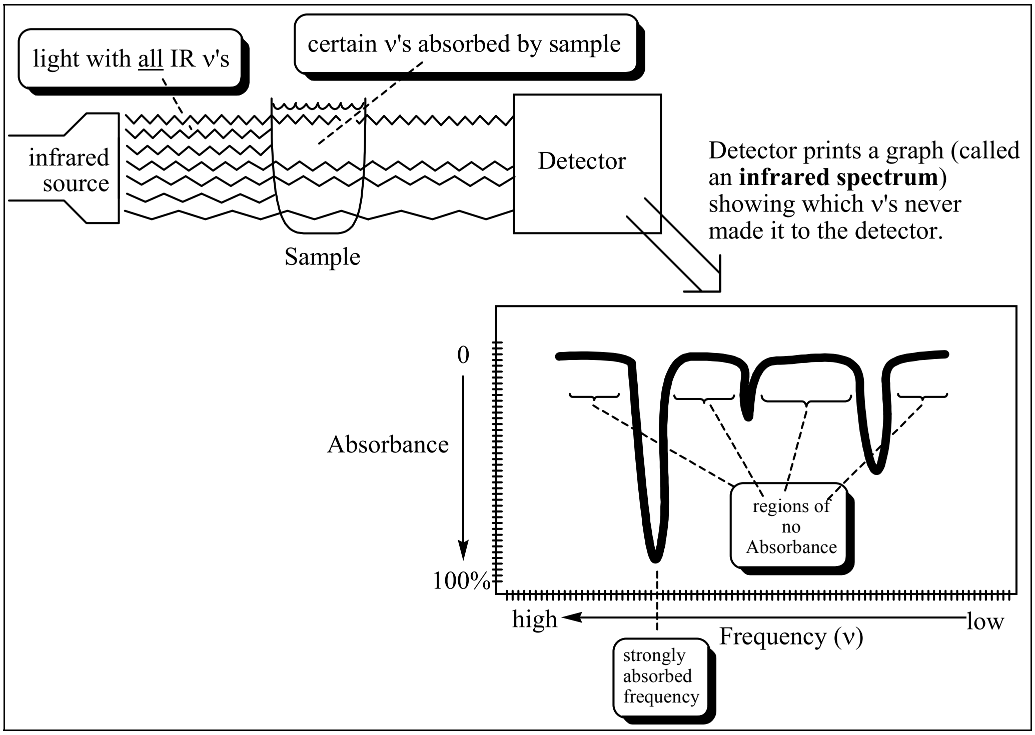

light with all IR ν's
certain ν's absorbed by sample
infrared source
Detector
Sample
Detector prints a graph (called an **infrared spectrum**) showing which ν's never made it to the detector.
0
Absorbance
100%
regions of no Absorbance
high
Frequency (ν)
low
strongly absorbed frequency

Figure L1.4: Diagram of Infrared Spectrometer

By convention, IR spectra are printed upside-down, so the peaks look like valleys. Another thing to look out for is that the x axis is marked in **wavenumbers**, also called **inverse centimeters** (cm^{-1}), instead of frequency (Hz). Since cm^{-1} are proportional to Hz, cm^{-1} are just another unit for frequency.

Critical Thinking Questions

12. What happened to the frequencies of light that never made it to the detector?

13. Assume that the light hitting the detector in Figure L1.4 is missing light of ν A, but is not missing light of ν B. Based on your conclusions at the top of this page, what structural features does the molecule in the sample tube have and not have?

Model 5: Sample IR Spectrum

An **infrared absorption frequency table** can be used to assign peaks to functional groups on the structure of an analyte molecule.

Critical Thinking Questions

14. Label each peak marked with an arrow on the spectrum with a type of bond found on the molecule in the box.

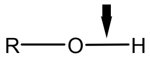
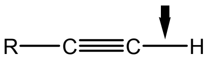
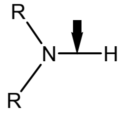
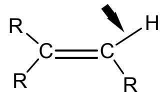
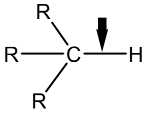
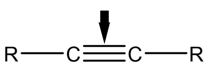
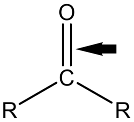
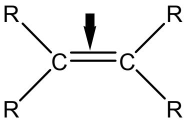
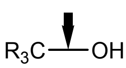
15. (Check your work.) The peak for an OH bond in Table L1.2 is described as "**broad**" and "**strong.**" Did you label the broadest strongest peak on the spectrum with an O—H? *[Note: Alcohol OH peaks have a characteristic "udder-like" shape.]*

16. The "**fingerprint region**" of an IR spectrum is often so crowded with peaks that it is hard to make assignments.

    a. In this case, which assigned peak falls in the fingerprint region?

    b. Speculate why it is called the fingerprint region.

Table L1.2: Characteristic IR Absorption Frequencies

Bond Description	**Example** (R = H or alkyl)	**Absorption Range** (cm^{-1})
alcohol O-H		3200–3650 (broad, strong)
alkyne C_{sp}–H		3260–3330
amine N—H		3100-3500
alkene C_{sp2}–H		3050–3150
alkane C_{sp3}–H		2840–3000 (strong)
alkyne C≡C		2100–2260
carbonyl C=O		1690–1760 (strong)
alkene C=C		1620–1680
alcohol C—O		1000–1260

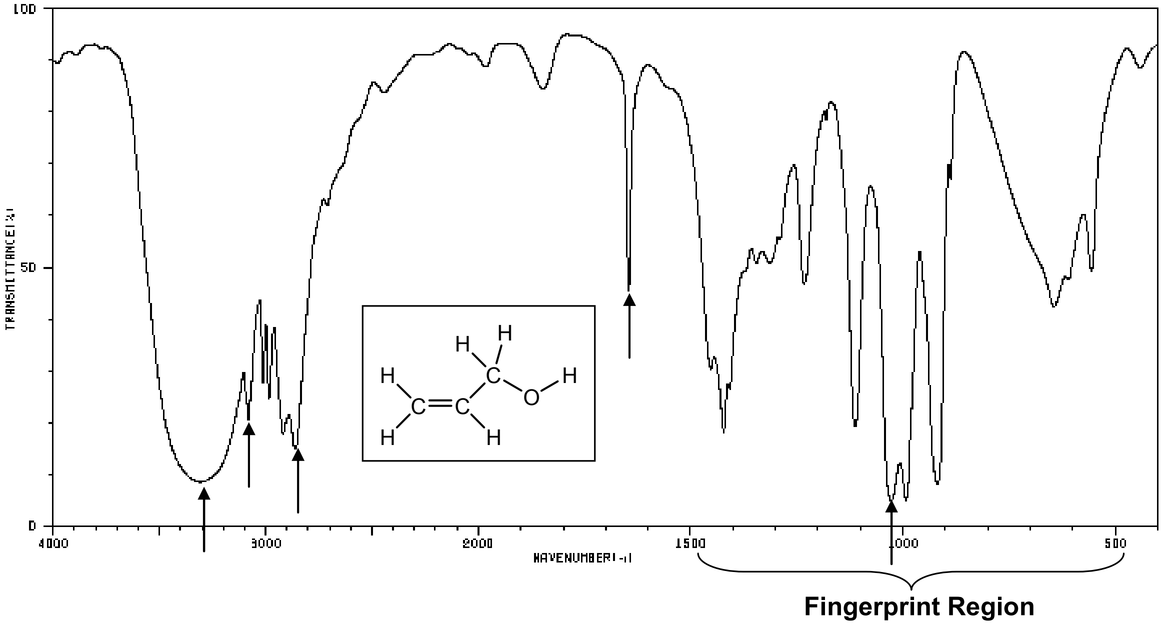


Figure L1.5: IR spectrum of prop-2-en-1-ol (structure shown in the box on the spectrum)

Term Introduction: Fingerprint Region = area on IR spectrum between 500-1500 cm^{-1}

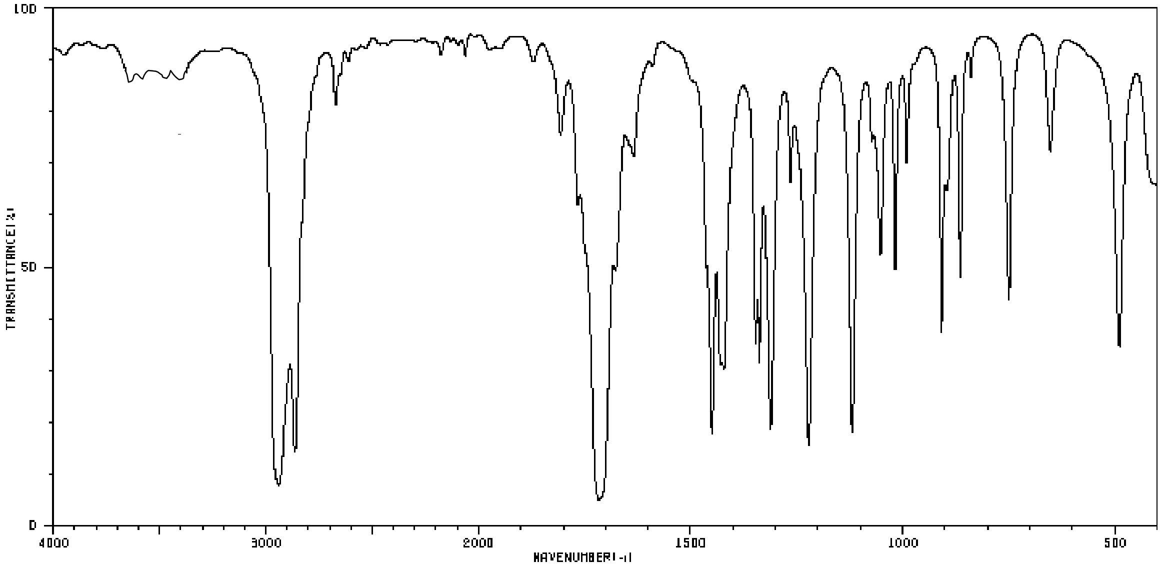
Two IR spectra of the same molecule should have matching fingerprint regions. Even though exact peak assignments are normally not made in this region, it can be used to identify a unique molecule much as a fingerprint is used to identify a unique person.

Memorization Task L1.1: Know the characteristic absorptions in Table L1.2.

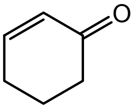
Memorize Table L1.2 so that you can identify bonds that are present in an unknown molecule based on its infrared spectrum.

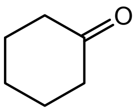
Critical Thinking Questions

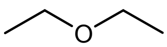
17. The IR spectrum below goes with one of the four structures shown. Circle the structure that goes with the IR spectrum.

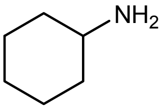


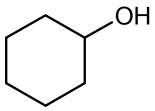
$H-C\equiv C-CH_2CH_2CH_3$











18. Match peaks in the spectrum above to two different types of bonds on the structure you circled.

19. You cannot draw the structure of an unknown molecule based on only information from an IR spectrum. Summarize what information an IR spectrum can give you about an unknown molecule.

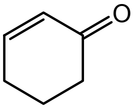
Check Your Work:

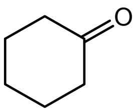
The Exercises for this activity contain the IR spectra of the other structures on this page.

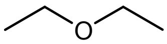
Exercises

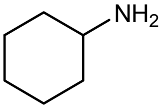
1. Cross out the structure below that you circled on the previous page. The IR spectra of the other structures are printed on the next two pages. **Draw the correct structure on each spectrum**, and assign each major peak outside the fingerprint to a bond in the structure by drawing a line from the bond to the peak associated with it.

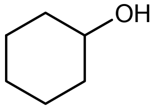
$H{-}C{\equiv}C{-}CH_2CH_2CH_3$

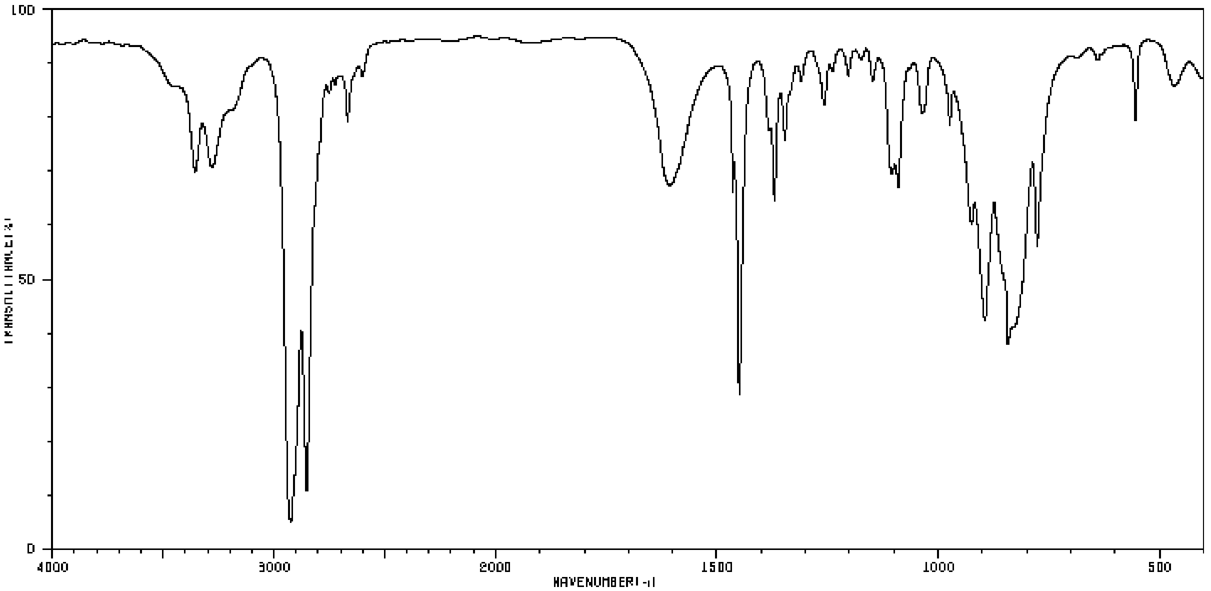


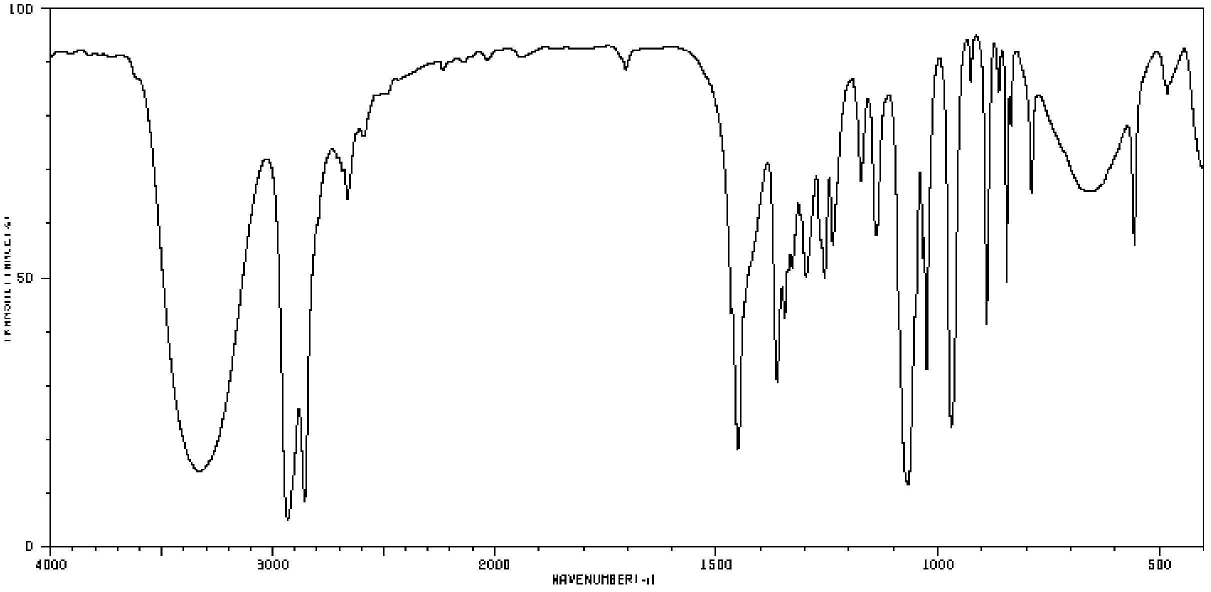


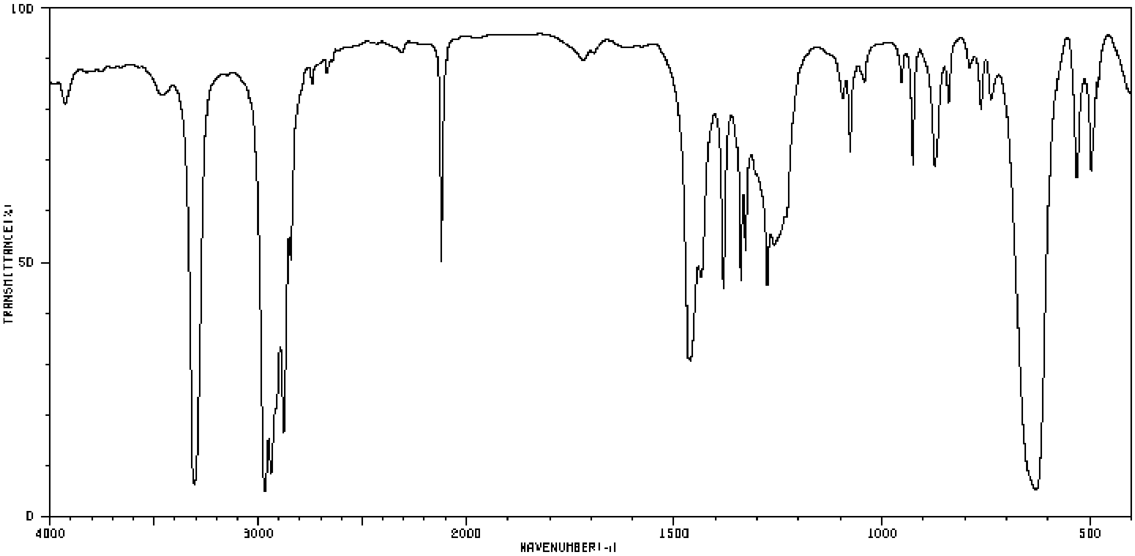











100
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TRANSMITTANCE[%]
4000
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2000
1500
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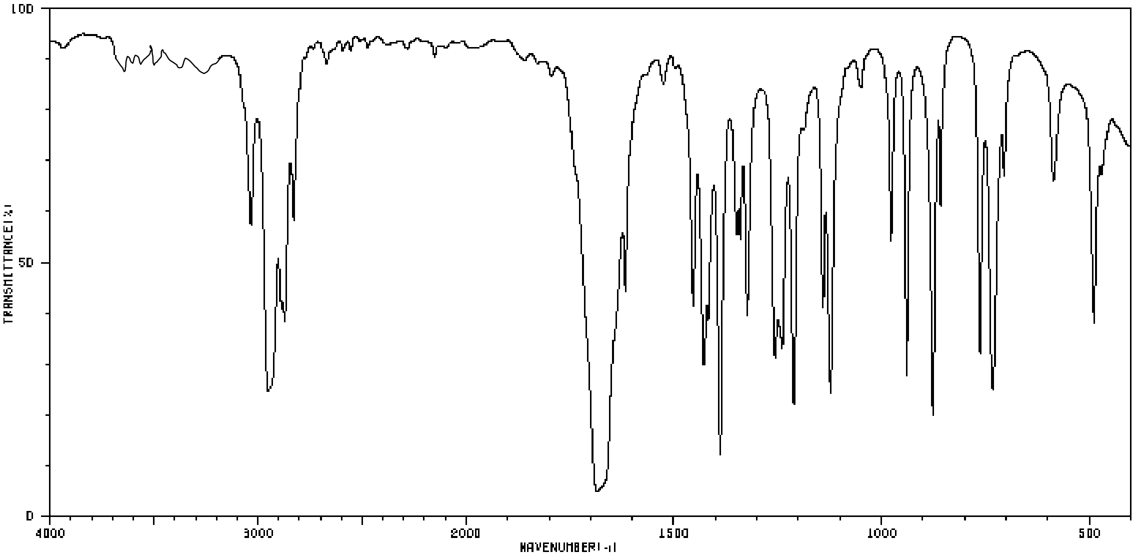
WAVENUMBER[-1]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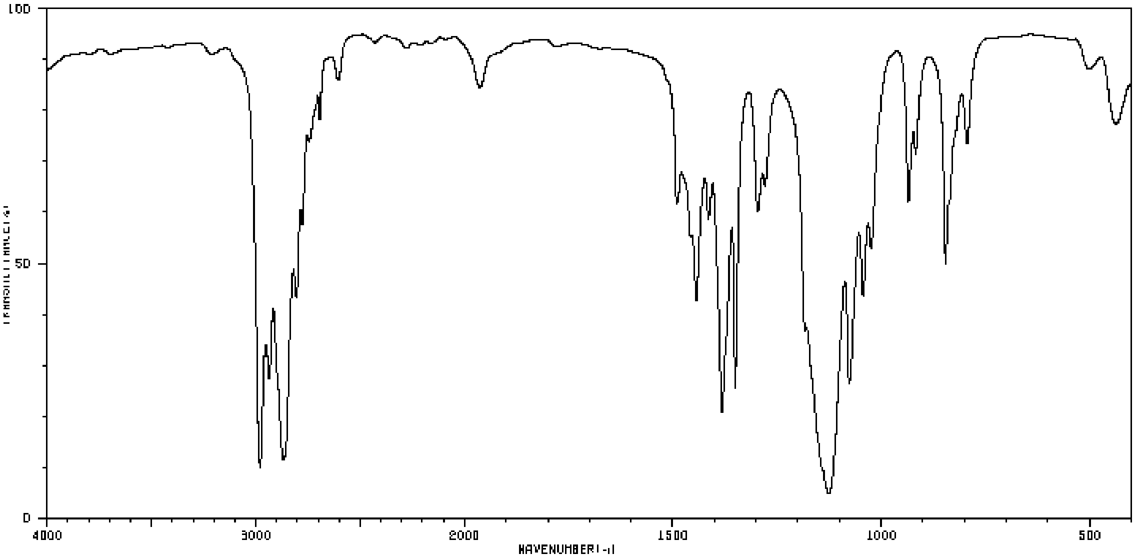
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2. Construct an explanation for why C—O has a much lower (slower) resonant absorption frequency than O—H, even though they have about the same bond strength (same "spring" strength).

3. Read the assigned pages in the text, and do the assigned problems.

The Big Picture

How do chemists know what molecules look like if they are too small to see with even the most advanced microscope? The answer is spectroscopy. Basically, we shine light of various frequencies on a pure sample of a molecule, and based on what happens to that light we can make various inferences about the structure of the molecule. IR spectroscopy is the first of several spectroscopic methods we will study in this course. The next one, called NMR, is much more powerful and will (unlike IR) allow us to elucidate the entire structure of some simple molecules.

Common Points of Confusion

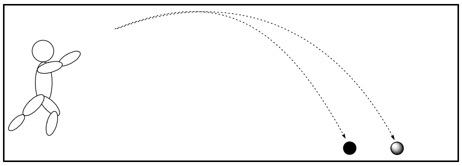
- One big problem with IR for students is that the peaks are upside-down, making the peaks look like valleys.
- The biggest problem with IR for students is that they assume the following: If there is a peak on the spectrum in a given range, there MUST be a specific functional group in the molecule they found on a table that corresponds to that frequency. Instead, IR peaks should be used as corroborating evidence of the existence of certain functional groups. The only possible exception to this rule is that the existence of OH and C=O functional groups can usually be definitively read from an IR spectrum.
- Another problem is that the units are confusing. **Wavenumbers** or **inverse centimeters** (cm^{-1}) are simply measures of frequency. Higher wavenumber → higher frequency.
- Students sometimes assume that they should be able to deduce the structure of an unknown molecule simply by looking at the IR spectrum. As we will see later, molecules are identified by using a combination of various different spectroscopic methods. IR simply tells you whether certain characteristic bonds (functional groups) are present in the unknown molecule.

ChemActivity L2: Mass Spectrometry

(How can we determine the mass and molecular formula of an unknown compound?)
This activity is designed to be completed in a 1 ½-hour laboratory session or two classroom sessions.

Model 1: Frictionless, Tireless, Reproducible Shot-Putter

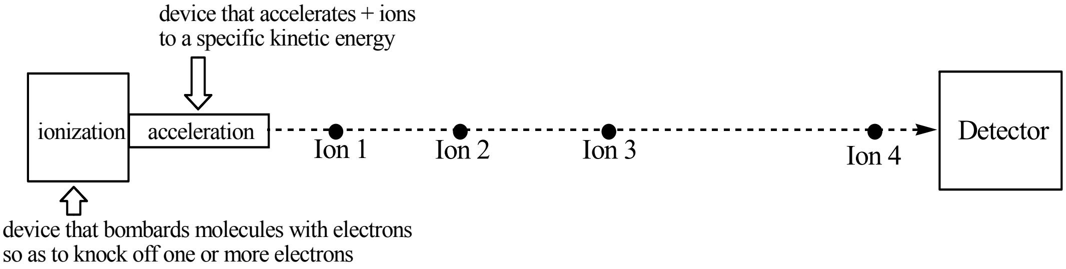
A shot-putter throws two balls with all her might. Assume the distance each ball goes is an exact and reproducible quantity (i.e., a 10-lb ball always goes the same distance, and she never gets tired. Ball 1 weighs 15 lbs; Ball 2 weighs 10 lbs.



Critical Thinking Questions

1. To show which ball went farther, label the 10- and 15-lb balls drawn in Model 1.
2. Given a set of balls of known weight, could you use the shot-putter in Model 1 to figure out the weight of a ball of unknown weight? Explain.

Model 2: Schematic of "Time of Flight" Mass Spectrometer


device that accelerates + ions
to a specific kinetic energy
ionization
acceleration
Ion 1
Ion 2
Ion 3
Ion 4
Detector
device that bombards molecules with electrons
so as to knock off one or more electrons

Critical Thinking Questions

3. The drawing in Model 2 represents a moment in time shortly after all four ions were *simultaneously* fired from the ion accelerator. All four ions have the same initial kinetic energy (KE = ½ mass x velocity^2) as they leave the ion gun, but Ion 4 hits the detector first, and Ion 1 hits the detector last. Which ion is most massive and which least massive?

4. Could you use the device in Model 2, a very accurate clock, and a set of ions of known mass to figure out the mass of an unknown molecule? Explain.

5. Mass spectrometers do not tell you directly the mass of an ion, but rather the ratio of the mass of an ion (*m*) divided by its charge (*z*): "**m/z**". *In this activity we will consider only the mass spectral data of +1 ions. This means you can assume that **m/z = mass**.*

   a. What is the mass of a +1 ion with *m/z* = 16?

   b. Draw the structure of a simple organic molecule with a mass of 16 amu.

Model 3: Ionization and Fragmentation

Most mass spectrometers accelerate a molecule by first turning it into an ion, then using an electric field to accelerate it toward the detector.

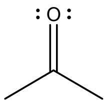
During standard ionization, a molecule loses one electron, the electron that is easiest to remove. The following is a hierarchy of electrons from easiest to hardest to remove:

- Electron in a lone pair (easiest)
- Electron that is part of a double bond (pi bond)
- Electron in a single bond (hardest)

Knocking off an electron to make a +1 ion can be a harsh process. This harsh treatment often results in a broken bond, generating two smaller pieces, a +1 ion and a neutral fragment. (**Note that only the ion is accelerated and detected**.)

Critical Thinking Questions

6. If acetone is ionized, which electron is most likely to be knocked off? Replace this electron with a + (to indicate the missing electron) on the structure of acetone →

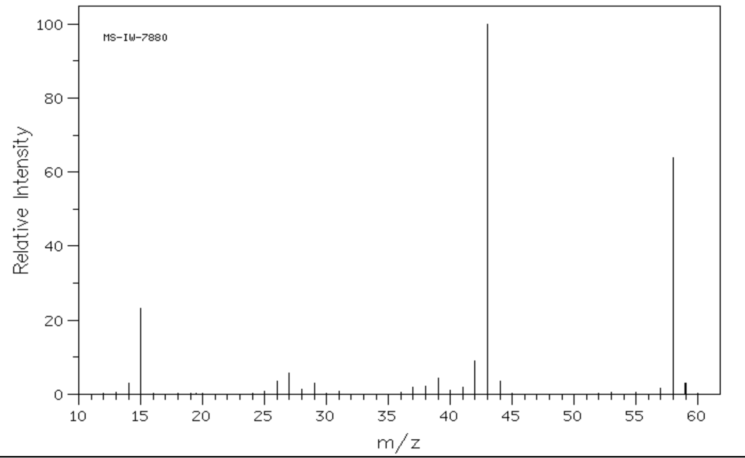


7. The ion you drew above is called the "**molecular ion**" of acetone. It is identical to the original molecule except that it is missing an electron, has a + charge, and can be accelerated by the mass spectrometer. What is the weight (in amu) of the molecular ion of acetone? (report only two significant figures, e.g., XX amu)

Model 4: Mass Spectrum of Acetone

The **mass spectrum** of acetone is a tally of the number of ions of each mass (*m/z*) that hit the detector when a large number of acetone molecules are run through the mass spectrometer. The **peak intensity** (peak height) tells you the relative number of ions of that weight that hit the detector.

m/z	Peak Intensity
14.0	2.9
15.0	23.1
26.0	3.5
27.0	5.7
29.0	3.1
38.0	2.2
39.0	4.2
41.0	2.0
42.0	9.1
43.0	100.0
44.0	3.4
58.0	63.8
59.0	3.1



Critical Thinking Questions

8. Label the peak due to the "**molecular ion**" of acetone with $\mathbf{[M]^+}$ (symbol for a molecular ion).

9. What is the peak intensity (relative height) of the $\mathbf{[M]^+}$ peak in this spectrum?

10. What is the weight (*m/z*) and intensity (height) of the most common ion detected during this mass spectrometry experiment? (This will be the tallest peak on the mass spectrum.)

Memorization Task L2.1: Base Peak vs. Molecular Ion

Warning! The **$[M]^+$ peak** (molecular ion) is often NOT the same as the base peak (largest peak).

The **base peak** is easy to identify since it is always the largest peak (by convention set to 100).

The $[M]^+$ peak (molecular ion) is easy to identify if you know the structure of the analyte (e.g., acetone).

Note: It can be hard to identify the $[M]^+$ peak on the mass spectrum of an unknown molecule. Much of this activity will be devoted to figuring out how to identify the $[M]^+$ peak on the MS of an unknown.

11. For some spectra, the base peak is the same as the $[M]^+$ peak. Is this the case for the spectrum of acetone shown on the previous page?

12. What is the size (in amu) of the neutral fragment that was lost to give the ion responsible for the base peak at *m/z* = 43?

    a. What combination of atoms weighs the amount you reported above, and whose loss could account for the peak at *m/z* = 43?

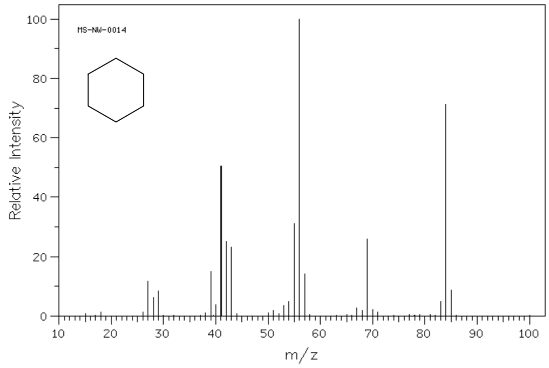
    b. Construct an explanation for why the peak at *m/z* = 43 is called the $[M\text{-}15]^+$ peak.

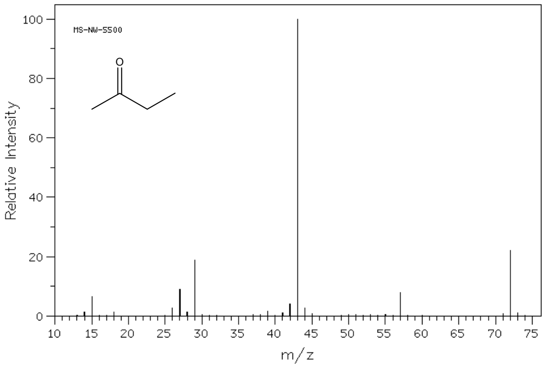
    c. Using the same naming strategy, name the peak on the mass spectrum at *m/z* = 15.

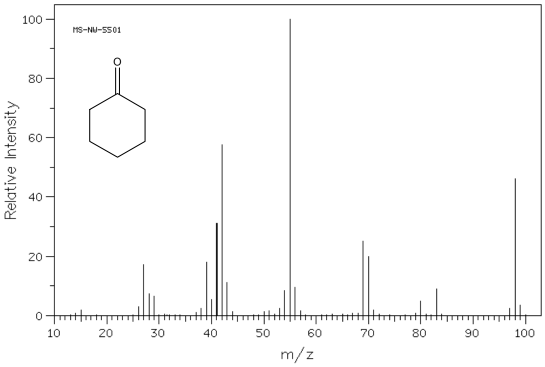
13. The major peaks on a mass spectrum representing ions lighter than the molecular ion are called **fragment peaks**. Draw an ion that could account for $[M\text{-}15]^+$ peak in the mass spectrum of acetone.

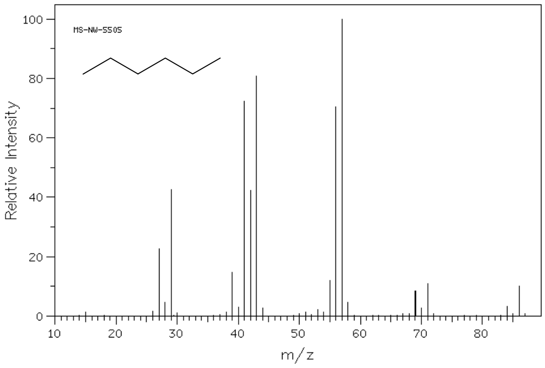
14. Shown below are the mass spectra (without data tables) of four molecules. (The structure of each molecule is shown on the spectrum.)

    a. Mark the **$[M]^+$ peak** for each, and indicate the molecular weight of the molecule.









    b. Based on the five mass spectra you have seen, describe how one might identify the $[M]^+$ peak (**molecular ion peak**) on the mass spectrum of an unknown compound.

Model 5: Isotope Natural Abundances

Atom	Most common isotope	Jump in Mass (no. extra neutrons)	Next most common isotope (no. found for every 100 atoms of most common isotope)
C	^{12}C (100)	+1	^{13}C (1.11)
O	^{16}O (100)		^{18}O (0.20)
S	^{32}S (100)		^{34}S (4.40)
N	^{14}N (100)		^{15}N (0.38)
Cl	^{35}Cl (100)		^{37}Cl (32.5)
Br	^{79}Br (100)		^{81}Br (98.0)

For example: There are 1.11 ^{13}C atoms on the planet for every 100 ^{12}C atoms. Equivalent ways of saying this are: There are likely to be 111 ^{13}C atoms in a sample of 10,111 carbon atoms or 1.10% of the carbon on the planet is ^{13}C (since 111/10,111 x 100% = 1.10%).

Critical Thinking Questions

15. What does the superscript to the left of each atom label tell you (e.g., the 12 in ^{12}C)?

16. Consider the data in Model 5:
    a. What is the mass of the most common isotope of carbon?
    b. What is the mass of the next most common isotope of carbon?
    c. The extra mass in ^{13}C is due to an extra neutron. Complete the chart by writing in the other **number of extra neutrons** needed to make each "next most common isotope."

17. If you were to randomly choose one methane molecule (CH_4) on this planet, what mass (in amu) is it **most likely** to have?

18. Given a sample of methane (CH_4) molecules, what percentage will contain a ^{13}C atom (i.e., $^{13}CH_4$) and weigh 17 amu?

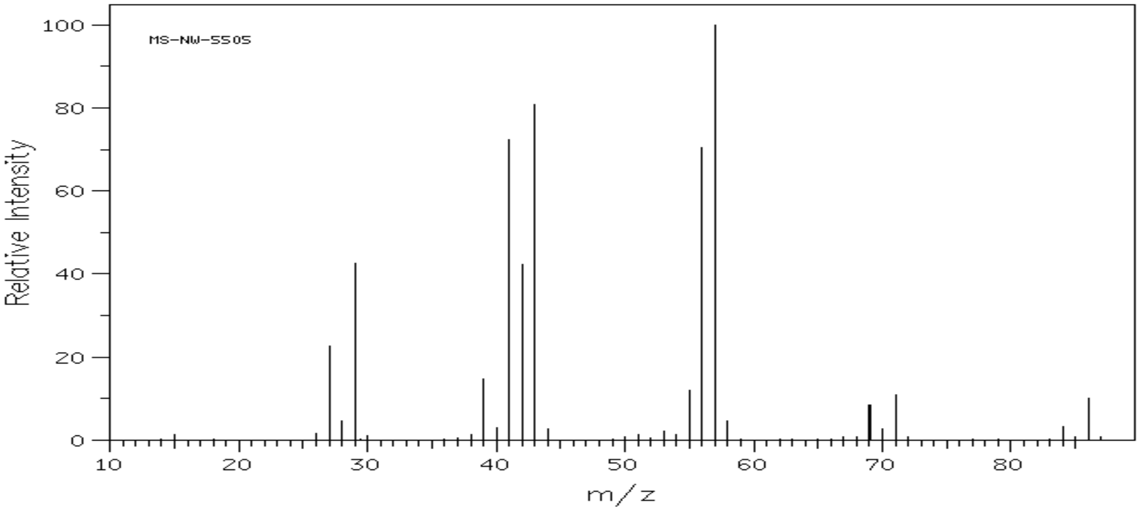
19. Imagine a barrel of raffle tickets. 1.1% of the tickets in the barrel are winners.
    a. What is your **percent chance** of winning if you buy **one** ticket?
    b. What is your **percent chance** of winning if you buy **two** tickets?
    c. What is your **percent chance** of winning if you buy **six** tickets?

20. Imagine that you are building models of alkanes (e.g., methane, ethane, hexane) using a huge bag of C atoms, 1.1% of which are marked with a "13" to indicate they represent ^{13}C atoms.
    a. How many times do you reach into the bag if you are building a model of methane? …ethane? …hexane?
    b. In a sample of ethane molecules (CH_3CH_3), 2.2% of the molecules are expected to contain one ^{13}C atom. What percentage of propane ($CH_3CH_2CH_3$) molecules will contain one ^{13}C atom? Explain your reasoning.

21. In a sample of hexane molecules (CH_3-CH_2-CH_2-CH_2-CH_2-CH_3), for every 100 molecules in the sample that weigh 86 amu, how many will weigh 87 amu?
(Report your answer to two significant figures: X.X)

22. An unknown hydrocarbon has a molecular formula C_xH_y. For every 100 molecules in the sample that contain only ^{12}C atoms, there are 9.9 that contain exactly one ^{13}C atom. How many carbons are in the molecule? (i.e., What is the value of x?)

23. Consider the mass spectrum of hexane.



a. Label the $[M]^+$ peak. What is the value of *m/z* associated with this peak?

b. What is the mass of a hexane molecule that contains six ^{12}C atoms ($^{12}CH_3$-$^{12}CH_2$-$^{12}CH_2$-$^{12}CH_2$-$^{12}CH_2$-$^{12}CH_3$)?
Does this fit with the *m/z* value reported in part a of this question?

c. Draw a picture, like the one of “all ^{12}C hexane” above, of a molecule that can account for the existence of a peak at *m/z* = 87 in the mass spectrum of hexane.

d. (Check your work.) There are actually three acceptable answers to the previous question because there are three unique locations in a hexane molecule to replace a ^{12}C with a ^{13}C. If you have not already done so, draw the other two acceptable answers to the previous question.

e. The peak at *m/z* = 87 is called the **$[M+1]^+$ peak**. Construct an explanation for this name.

f. Use your periodic table to calculate the weight, in grams, of 1 mole of hexane to four significant figures (XX.XX).

g. Explain why 1 mole of hexane weighs slightly more than 86 grams.

Model 6: Intensities of $[M+1]^+$ Peak and $[M+2]^+$ Peak

On a mass spectrum, the height of given peak is proportional to the number of molecules with that mass. Note that in the table below the $[M]^+$ peak happens to be the base peak.

Molecule	$[M]^+$ *m/z* (intensity)	$[M+1]^+$ *m/z* (intensity)	$[M+2]^+$ *m/z* (intensity)
Methane	16 (100)	17 (1.1)	NA
Ethane	30 (100)	31 (2.2)	NA
Propane	44 (100)		NA
Butane	58 (100)		NA
Octane	114 (100)		NA
Bromomethane CH_3Br	94 (100) $^{12}CH_3{}^{79}Br$		
Bromoethane CH_3CH_2Br	108 (100)		
Chloromethane CH_3Cl	50 (100)		
Chloroethane CH_3CH_2Cl	64 (100)		

Critical Thinking Questions

24. Fill in the *m/z* values for the $[M+1]^+$ column in Model 6.

    a. Explain why the intensity of the $[M+1]^+$ peak for ethane is twice as high as the $[M+1]^+$ peak for methane. (*Hint*: Look back at CTQ's 18-22.)

    b. Fill in the $[M+1]^+$ intensities for all molecules in the table.

    c. **True** or **False**: When $[M]^+$ has an intensity of 100, the following formula can be used to calculate the number of carbons in the molecule.

$$\boxed{\text{number of carbon atoms} = \frac{\text{intensity of }[M+1]^+\text{ peak}}{1.1}}$$

Memorization Task L2.2: Formula for calculating number of carbons from $[M+1]^+$ intensity

$$\boxed{\text{number of carbon atoms} = \left(\frac{\text{intensity of }[M+1]^+\text{ peak}}{1.1}\right) \text{ x } \left(\frac{100}{\text{intensity of }[M]^+\text{ peak}}\right)}$$

This $[M+1]^+$ **formula** can be used regardless of the intensity of the $[M]^+$peak.

    d. Confirm that the formula in Memorization Task L2.2 reduces to the one in part c of this question when $[M]^+$ has an intensity of 100.

Memorization Task L2.3: Formula for calculating number of oxygens from $[M+2]^+$ intensity

$$\text{number of oxygen atoms} = \left(\frac{\text{intensity of } [M+2]^+ \text{ peak}}{0.2}\right) \times \left(\frac{100}{\text{intensity of } [M]^+ \text{ peak}}\right)$$

25. The formula in Memorization Task L2.3 can be used to calculate the number of oxygen atoms in a molecule. By analogy to these two formulas, fill in the blanks in Memorization Task L2.4 to give a formula for calculating the number of sulfur atoms in an unknown molecule.

Memorization Task L2.4: Formula for calculating number of sulfurs from $[M+\_\_]^+$ intensity

$$\text{number of sulfur atoms} = \left(\frac{\rule{4cm}{0pt}}{\rule{4cm}{0pt}}\right) \times \left(\frac{\rule{4cm}{0pt}}{\rule{4cm}{0pt}}\right)$$

Note that the formulas above work only when only one element is making a significant contribution to the $[M+1]^+$ or $[M+2]^+$ peak. For example, as we will see in the next section, you cannot use the formula to calculate the number of oxygen or sulfur atoms when there is a Cl or Br present.

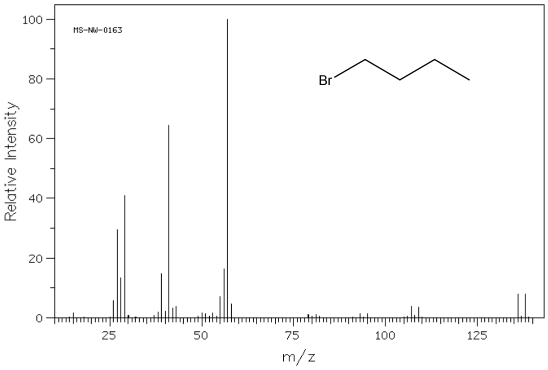
26. Fill in *m/z* values in the $[M+2]^+$ column in Model 6.
    a. For each compound containing Br or Cl, draw the most common molecule responsible for each peak in that row. Be sure to include isotopic labels for each nonhydrogen atom (The first box is done for you.) (*Hint*: Look back at the entries for Br and Cl in Model 5.)
    b. Fill in the intensities for each box in the $[M+2]^+$ column.
    c. Why is there no significant $[M+2]^+$ peak for the first five rows?

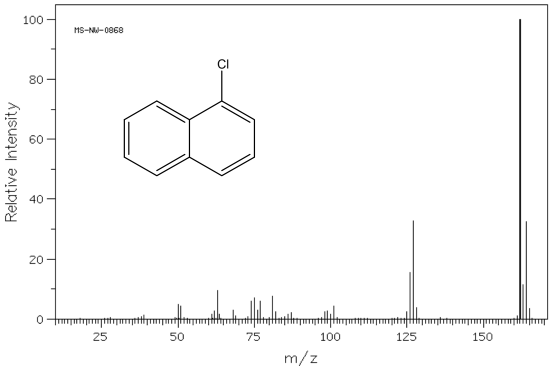
    d. What elements other than Cl and Br will generate a noticeable $[M+2]^+$ peak? (*Hint*: Look at the table in Model 5.)

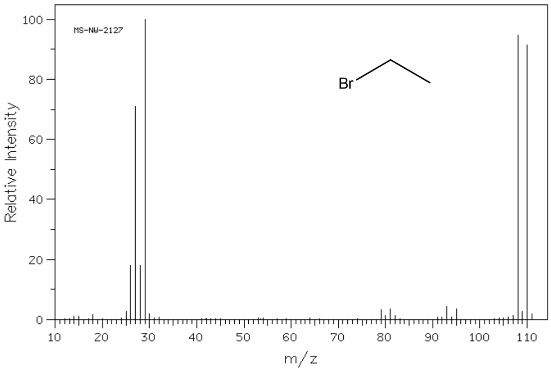
    e. Fill in the blanks in the following two statements:
        (1) If the intensities of the $[M+2]^+$ and $[M]^+$ peaks are approximately equal, then there is likely one ______ atom in the molecule.
        (2) If the intensity of the $[M+2]^+$ peak is about one-third that of the $[M]^+$ peak, there is likely one ______ atom in the molecule.

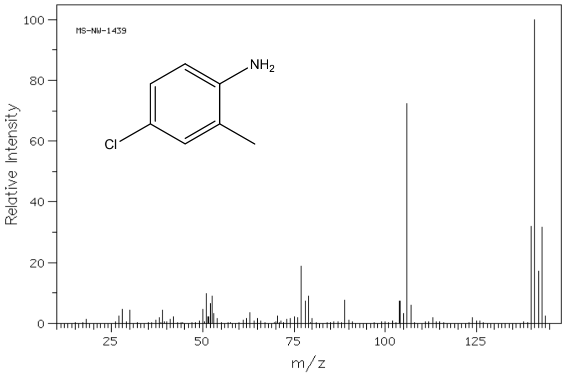
27. The rule you generated in Question 14b for finding the $[M]^+$ peak on the mass spectrum of an unknown molecule does not work very well if there is a Br or Cl in the molecule. Shown below are spectra of various compounds containing one Br or Cl.

    a. Find the $[M]^+$ and **$[M+2]^+$ peak** on each spectrum.









    b. Write a rule for quickly identifying from a mass spectrum if an unknown molecule has…

        (1) one Cl atom.

        (2) one Br atom.

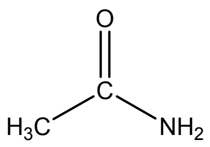
Note: The mass spectrum of a molecule with more than one Cl or Br can be quite complex, so we will limit cases to one Cl or Br.

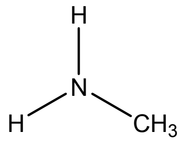
    c. Write a new rule for finding the $[M]^+$ peak that takes into consideration the fact that Br and Cl have very large $[M+2]^+$ peaks.

28. Each of the spectra above contains an $[M+3]^+$ peak. This peak arises because ^{37}Cl and ^{81}Br are so common that there are a significant number of ions with a heavy isotope of both carbon and the halogen, e.g, [one ^{13}C and one ^{37}Cl] or [one ^{13}C and ^{81}Br]. Mark this $[M+3]^+$ peak on each spectrum above.

29. On the mass spectrum of hexane in this activity, the $[M]^+$ peak (at *m/z* = 86) has an intensity of 10. Calculate the expected intensity of the [M+1] peak in this spectrum.

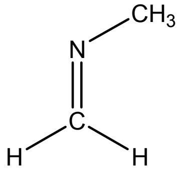
30. Calculate the molecular weight of each of the following molecules using the most common isotope of each element:





NH_3

$N\equiv C-H$



31. What do the molecular weights in the previous question have in common with one another that set them apart from ALL the molecular weights in the $[M]^+$ column in Model 6?

Memorization Task L2.5: Nitrogen Rule

It turns out that any molecule with an odd number of nitrogen atoms (1, 3, 5, etc.) will have an odd molecular weight and vice versa. This "**nitrogen rule**" is a consequence of the fact that ^{14}N is the only common organic element that makes an odd number of bonds but has an even molecular weight.

32. Give examples of two very common elements that make an even number of bonds and whose most common isotope has an even molecular weight.

33. Give an example of at least one element that makes an odd number of bonds and whose most common isotope has an odd molecular weight.

Exercises

1. Consider the following peak heights for an unknown compound:

Ion	*m/z*	Intensity
$[M]^+$	176	50.1
$[M+1]^+$	177	5.5
$[M+2]^+$	178	16.7

a. What is the mass (in amu) of the most abundant isotope of this molecule? In other words, what is the molecular weight calculated using the most common isotope of each atom?

b. How many carbons are there in this molecule? How can you tell? **Note: MS calculations of the number of carbons may not be accurate. You should always consider the possibility of one more or one fewer carbon atoms than the calculated number.**

c. Is there evidence of atoms other than C and H in this molecule? What are they, and how can you tell?

d. Is there an odd number of nitrogen atoms? How can you tell?

e. Is it possible in this case to have two N atoms and still weigh 176 amu?

f. If you assume the molecule is composed only of carbon, one chlorine and hydrogen, how many H's are there in the molecule? How can you tell?

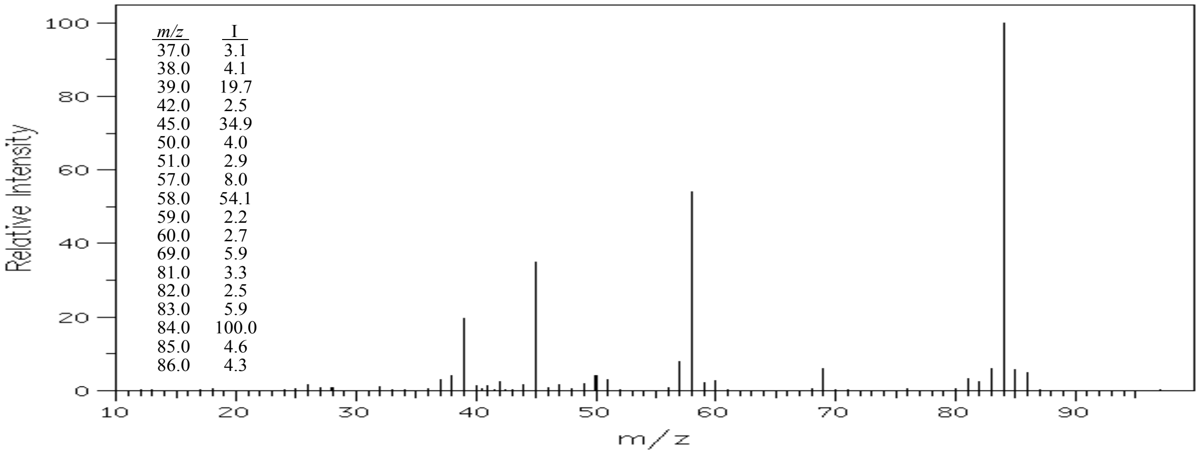
g. What is the likely molecular formula of this molecule?

h. Draw a neutral molecule with this molecular formula. (If you cannot do this, you have made an error or need to start again with one more or one fewer carbon. See b above.)

i. Can you tell for sure the structure of this molecule based on this MS data?

2. We normally ignore the contribution of deuterium to the $[M+1]^+$ peaks. Is this statement consistent with the fact that ^2H (deuterium) makes up only 0.0162 % of the hydrogen on earth? We also ignore the contribution of $^{13}CH_3$-$^{13}CH_3$-^{79}Br to the $[M+2]^+$ peak of bromoethane. Explain.

3. Consider the following mass spectrum of an organic unknown.



m/z	I
37.0	3.1
38.0	4.1
39.0	19.7
42.0	2.5
45.0	34.9
50.0	4.0
51.0	2.9
57.0	8.0
58.0	54.1
59.0	2.2
60.0	2.7
69.0	5.9
81.0	3.3
82.0	2.5
83.0	5.9
84.0	100.0
85.0	4.6
86.0	4.3

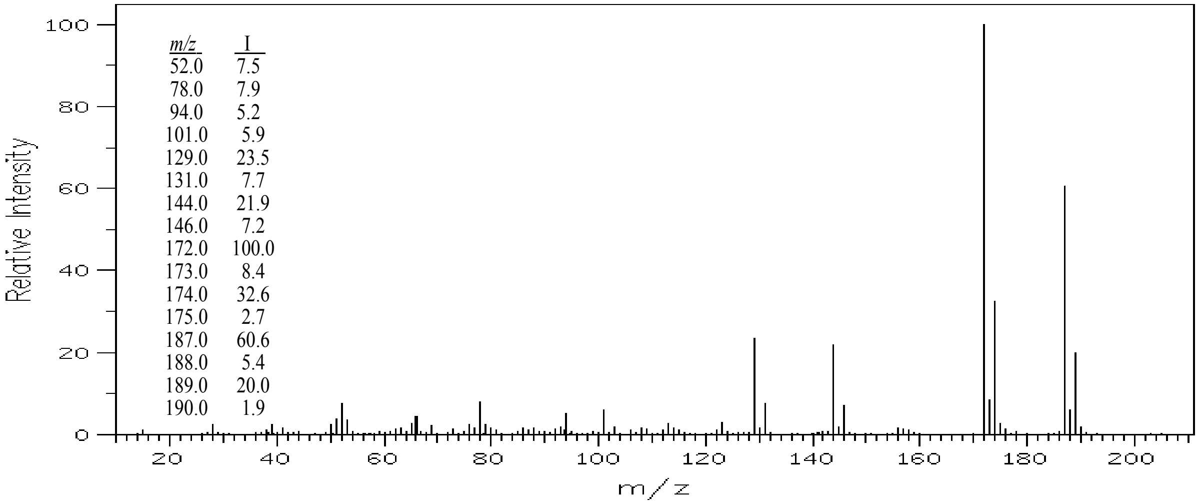
a. Determine the molecular formula.

b. Mark the **$[M]^+$, $[M+1]^+$, $[M+2]^+$** peaks (if present).

c. Mark the largest fragment peak with its name.

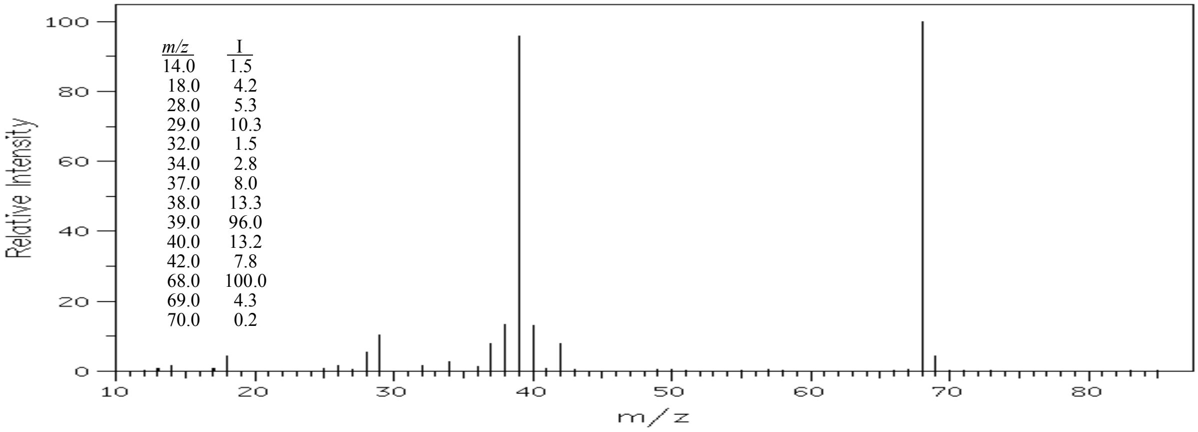
d. Briefly summarize the information that can be obtained from these peaks.

4. Determine the molecular formula that goes with the following mass spectrum, and draw a possible structure that goes with this formula.



m/z	I
52.0	7.5
78.0	7.9
94.0	5.2
101.0	5.9
129.0	23.5
131.0	7.7
144.0	21.9
146.0	7.2
172.0	100.0
173.0	8.4
174.0	32.6
175.0	2.7
187.0	60.6
188.0	5.4
189.0	20.0
190.0	1.9

5. Consider the following mass spectrum of an organic unknown.



m/z	I
14.0	1.5
18.0	4.2
28.0	5.3
29.0	10.3
32.0	1.5
34.0	2.8
37.0	8.0
38.0	13.3
39.0	96.0
40.0	13.2
42.0	7.8
68.0	100.0
69.0	4.3
70.0	0.2

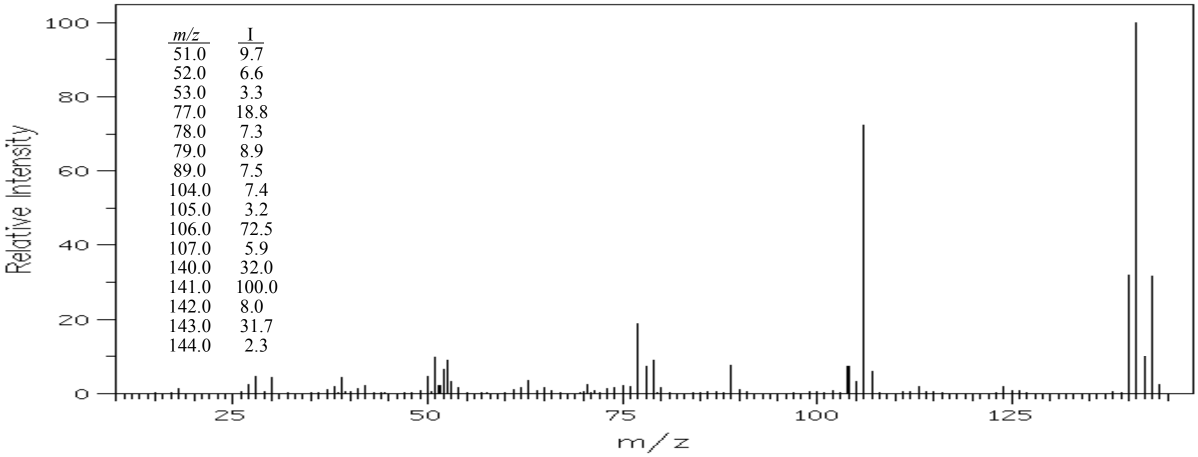
a. Determine the molecular formula. **Write the formula on the spectrum.**

b. Mark the **$[M]^+$, $[M+1]^+$, $[M+2]^+$** peaks (if present).

c. Mark the largest fragment peak with its name.

d. Draw the structure of a neutral molecule with the molecular formula above.

6. Determine the molecular formula that goes with the following mass spectrum. Write this on the spectrum, and draw a structure that fits with this molecular formula.



m/z	I
51.0	9.7
52.0	6.6
53.0	3.3
77.0	18.8
78.0	7.3
79.0	8.9
89.0	7.5
104.0	7.4
105.0	3.2
106.0	72.5
107.0	5.9
140.0	32.0
141.0	100.0
142.0	8.0
143.0	31.7
144.0	2.3

The Big Picture

Mass spectroscopy is often the first tool in determining the identity of an unknown compound because simple (low resolution) mass spectroscopy usually yields an accurate molecular formula.

More complex instruments can compare a spectrum to those of known molecules, giving a positive identification of an exact structure. This is how drug testing is carried out. This spectrum matching is similar to matching the fingerprint region of an IR spectrum, but much more accurate. One way this is done is to match **fragmentation patterns**. That is, a molecule falls apart in the same way each time, leaving telltale clues about its identity in the pattern of fragmentation peaks (peaks smaller than the $[M]^+$ peak).

Identification of fragmentation patterns can help you figure out the most likely structure or structures among the many isomeric possibilities. There is a science to predicting fragmentation patterns, but that topic is not covered in this activity. A simplistic (but often effective) way of predicting fragments is to chop up the molecule near any functional group.

Common Points of Confusion

- Students commonly make the error of assuming that the base peak gives the molecular weight of an unknown compound. The base peak is *sometimes* also the molecular ion, but more often these peaks are not the same. The only time they are the same is when the molecular ion is the most abundant ion detected, making the molecular ion peak the tallest peak in the spectrum.
- Do not make the mistake of assuming that a calculation of the number of carbon atoms based on the height of the **$[M+1]^+$ peak** is set in stone. Any calculation of the number of carbon atoms (or especially the number of oxygen, sulfur or other atoms) is subject to a high degree of error due to the usually small height of the $[M+1]^+$ (or **$[M+2]^+$) peak**. You should always consider the possibility that such calculated numbers could be off by +/- 1.

ChemActivity L3: Carbon (^{13}C) NMR Spectroscopy

BUILD MODELS: 1-bromo-2,3,3-trimethylbutane

(What can a ^{13}C NMR spectrum tell you about the structure of a molecule?)

This activity is designed to be completed in a 1-½-hour laboratory session or two classroom sessions.

Model 1: Spectroscopy Using Radio Waves

In the presence of an external magnetic field, a ^{13}C atom will absorb light in the radio frequency range. The precise frequency of the light absorbed tells us about the atoms near that carbon atom.

For example: the five different carbon atoms labeled **a to e** below absorb light of different frequencies. Frequency is measured along the x axis on the chart in funny units called **ppm**. Each cluster of peaks (labeled with a letter) indicates a unique carbon that absorbs light at that frequency.

When the light is absorbed, it causes what is called a **nuclear spin flip**, so this type of spectroscopy is called **nuclear magnetic resonance** (or **NMR**) spectroscopy.

NMR is the most widely used tool for determining the structure of molecules.

It turns out that the physics of NMR spectroscopy is quite complex. Since its discovery in the 1940s it has grown to become its own subfield of chemistry. The simplified explanation above will be enough for us to learn to interpret NMR spectra.

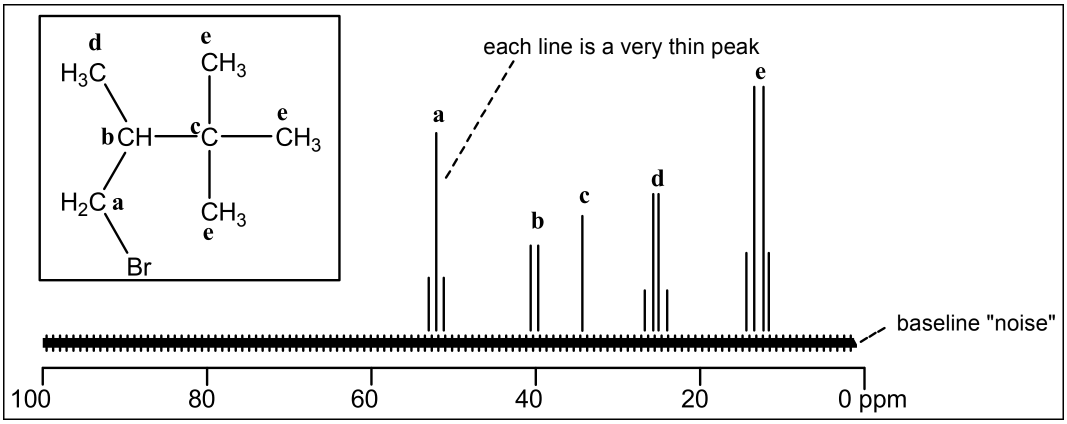


Figure L3.1: Cartoon of (coupled) ^{13}C NMR Spectrum of 1-bromo-2,3,3-trimethylbutane

Critical Thinking Questions

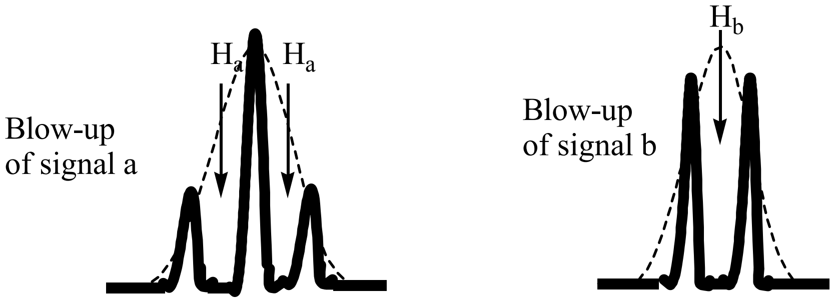
1. Next to each carbon in the structure, indicate the number of hydrogens attached to that carbon. Also write this number next to the corresponding **peak cluster** on the spectrum.

2. Construct an explanation for why the three carbon atoms labeled "**e**" are called equivalent carbons (or chemically indistinguishable carbons). A model may help. Note that the three carbons labeled "**e**" are also called **NMR equivalent**. This is because the peak clusters due to the three "e" carbons are on top of each other (appear as one large peak cluster) on the NMR spectrum in Figure L3.1.

3. Is there a relationship between the number of hydrogens attached to a given carbon and the number of peaks in the cluster associated with that carbon? If so, what is it?

Memorization Task L3.1: Peak Multiplicity = [Number of H's] + 1

Chemists say that "the two H atoms attached to C_a (we will call them H_a) '**split**' the signal of C_a into three peaks." This is the **multiplicity** of a peak and is illustrated in the diagram below for peak clusters a and b. The dotted line illustrates what the peaks would look like without any splitting.



2 H atoms "split" the signal due to C_a 1 H atom "splits" the signal due to C_b

A peak cluster with…

- **one** peak is called a **singlet (s)**
- **two** peaks is called a **doublet (d)**
- **three** peaks is called a **triplet (t)**
- **four** peaks is called a **quartet (q)**
- **five or more** peaks is called a **multiplet (m)**

Critical Thinking Questions

4. Label each peak cluster in Figure L3.1 with s, d, t, q, or m.

5. Which of the following best explains the placement of peak clusters along the x axis?
   a. The number of hydrogens attached to that carbon atom.
   b. The total number of bonds to that carbon atom.
   c. Distance from the Br atom (no. of bonds away from Br atom).

Memorization Task L3.2: Memorize the following ^{13}C NMR Chemical Shifts (ppm ranges)

The property measured by the x axis is called **chemical shift** (think of it as frequency). It is measured in strange units called **ppm**.

The chemical shift of an atom is related to the density of the electron cloud around that atom.

Chemical shift is hard to predict precisely. Memorize these **NMR ppm ranges (^{13}C)**.

Factors effecting chemical shift are additive. *E.g. alkene C attached to a halogen (C=**C**–Br) could be found above 150 ppm.*

Type of Carbon	**Examples** (R = H or alkyl)	**ppm Range**
C with all single bonds to C's or H's	**C**H_4 R_3**C**H	5-60
C with a single bond to O, N, or a halogen	R_3**C**—OH R_3**C**—Br	20-90
C with double/triple bond to C (e.g. C=C)	R_2C=**C**R_2	110-150
C with double bond to O (**C**=O)	R_2**C**=O R**C**O_2H	150-220

Critical Thinking Questions

6. Within the category of carbons singly bound to only C and H (5-60 ppm), quartets will appear between 5-30 ppm; triplets (15-50 ppm); doublets (25-60 ppm); and singlets (30-40 ppm). Are these refined ranges consistent with the chemical shifts of the peak clusters in Figure L3.1?

7. Consider the following ^{13}C NMR spectrum of 2-bromobutane. Label each peak cluster with a number (1, 2, 3, or 4) indicating its assignment to a specific carbon and a letter (s, d, t, or q).

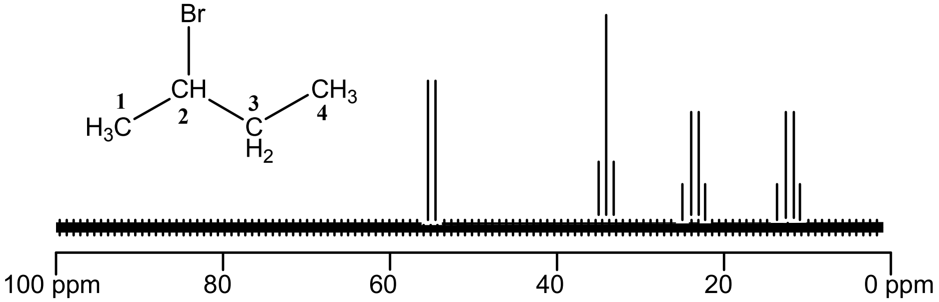


Figure L3.2a: Cartoon of (coupled) ^{13}C NMR Spectrum of 2-bromobutane

Model 2: NMR, Coupled versus Decoupled Spectra

If you have a complex molecule with several similar types of carbon atoms, the peak clusters generally overlap. This makes interpretation very difficult. To solve this problem, chemists "**decouple**" the H's from the C's. A **decoupled** ^{13}C NMR spectrum of 2-bromobutane is shown below.

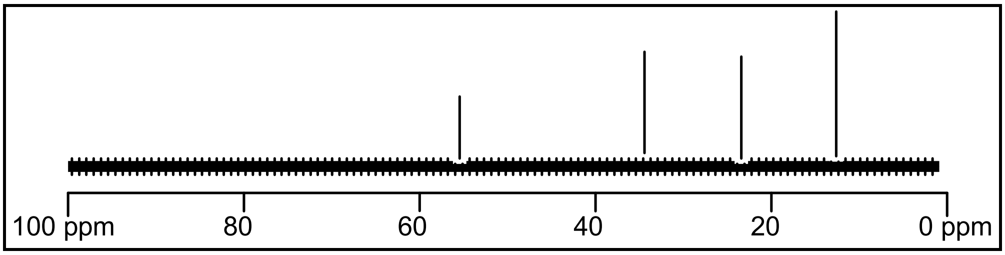


Figure L3.2b: Cartoon of *Decoupled* ^{13}C NMR Spectrum of 2-bromobutane

Think of each C–H bond as a phone link. In the coupled spectrum, each H is “talking to” the nearest carbon, “splitting” the carbon signal through this "phone link." To make a decoupled spectrum, we produce lots of static on the “phone line” so each carbon cannot “hear” the H’s attached to it. Consequently, each carbon shows up as a **singlet** (one peak). **You will probably never see a coupled ^{13}C NMR spectrum outside this activity.** *Their value as a teaching tool will be apparent in the next part.*

Critical Thinking Questions

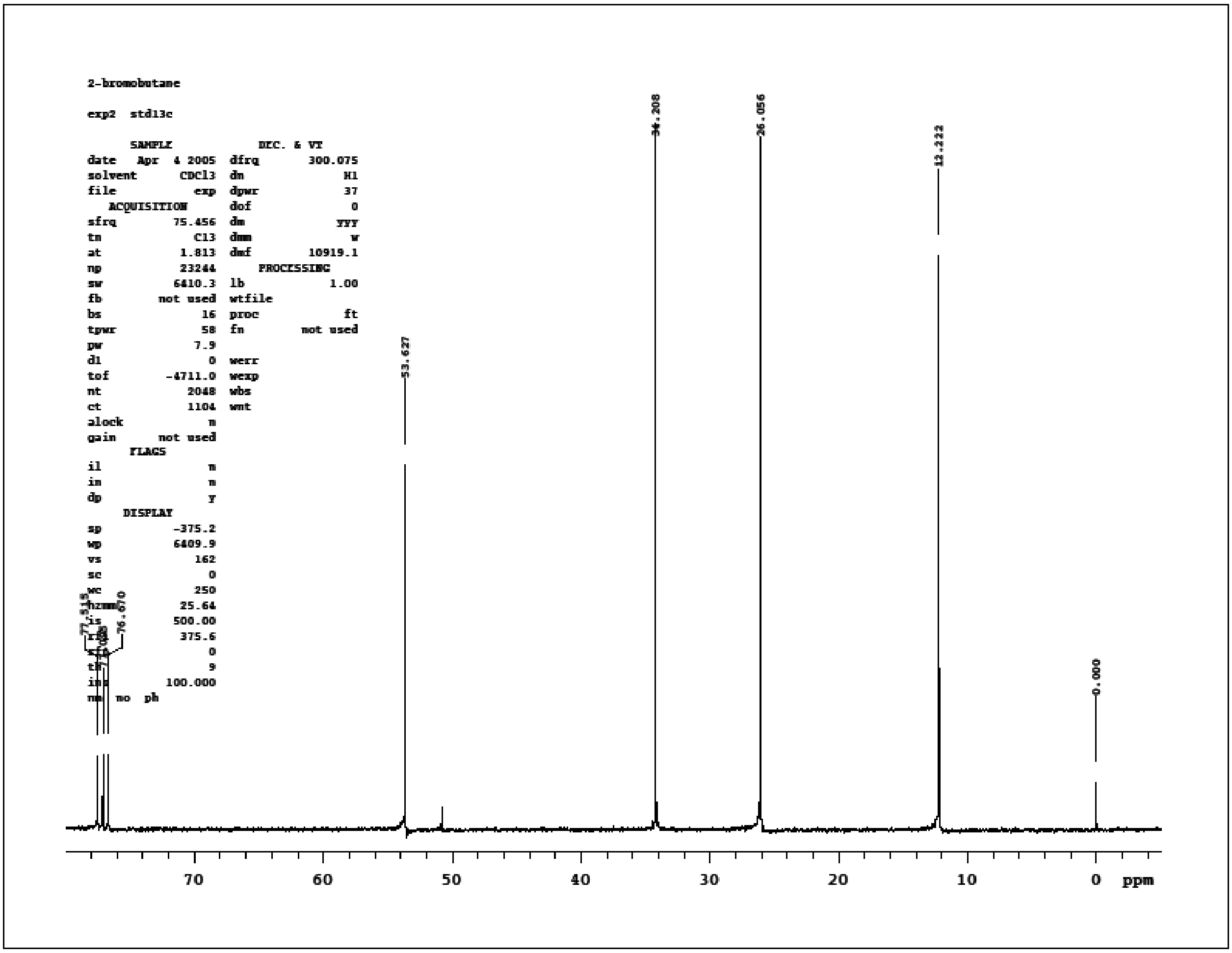
8. What structural information is lost when we decouple the C's from the H's?

9. What basic structural information does a decoupled ^{13}C NMR spectrum still convey?

10. **T** or **F**: In ^{13}C NMR the height of a peak is proportional to the number of equivalent carbons represented by that peak.

11. Sketch a reasonable (coupled) ^{13}C NMR spectrum for 3-methyl-1-pentene. Then, below it, sketch the decoupled spectrum. Don't worry about exact placement or relative order of the peak clusters. <u>Just make sure each peak cluster is in the right range</u>.

12. The NMR spectra in the previous sections are computer-generated cartoons. Shown below is a real decoupled ^{13}C NMR spectrum of 2-bromobutane. Label some differences between the computer-generated decoupled spectrum (Figure L3.2b) and the real version (Figure L3.3, below).

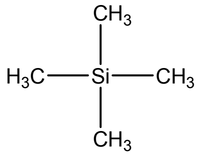


```
2-bromobutane

exp2  stdl3c

      SAMPLE              DEC. & VT
date   Apr  4 2005  dfrq        300.075
solvent       CDCl3  dn              H1
file            exp  dpwr            37
   ACQUISITION       dof              0
sfrq         75.456  dm             yyy
tn              C13  dmm              w
at            1.813  dmf        10919.1
np            23244       PROCESSING
sw           6410.3  lb            1.00
fb         not used  wtfile
bs               16  proc            ft
tpwr             58  fn        not used
pw              7.9
d1                0  werr
tof         -4711.0  wexp
nt             2048  wbs
ct             1104  wnt
alock             n
gain       not used
      FLAGS
il                n
in                n
dp                y
      DISPLAY
sp           -375.2
wp           6409.9
vs              162
sc                0
wc              250
hzmm          25.64
is           500.00
rfl           375.6
rfp               0
th                9
ins         100.000
nm   no   ph
```

Figure L3.3: Decoupled ^{13}C NMR Spectrum of 2-bromobutane

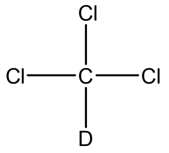
Memorization Task L3.3: NMR Reference and Solvent Peaks

On a ^{13}C NMR spectrum (also called a CMR spectrum) you will often see a peak at 0 ppm and three peaks centered at 77.0 ppm. **These peaks are associated with additives, not the analyte molecule.** The most common additives are **TMS** (a reference compound) and **$CDCl_3$** (a solvent).



$Si(CH_3)_4$

TMS (tetramethylsilane)
a reference compound that is often added to the sample because it is inert and gives a peak at 0 ppm that can be used calibrate the ppm scale



$CDCl_3$

$CDCl_3$ (deuterated chloroform)
a solvent that produces three small peaks centered at 77.0 ppm, where few other peaks appear (also can be used to calibrate the ppm scale)

Critical Thinking Questions

13. Label the peaks in Figure L3.3 due to TMS and $CDCl_3$ with these terms. Also label the impurity peak near 50 ppm that is not associated with the solvent, reference, or analyte (2-bromobutane).

Model 3: DEPT NMR

Figure L3.4 is a **DEPT** NMR spectrum of 2-bromobutane. A DEPT spectrum consist of **four spectra:** the top spectrum shows only carbons with three H's; the second shows only carbons with two H's; the third shows only carbons with one H; and the bottom shows all carbons with one or more H.

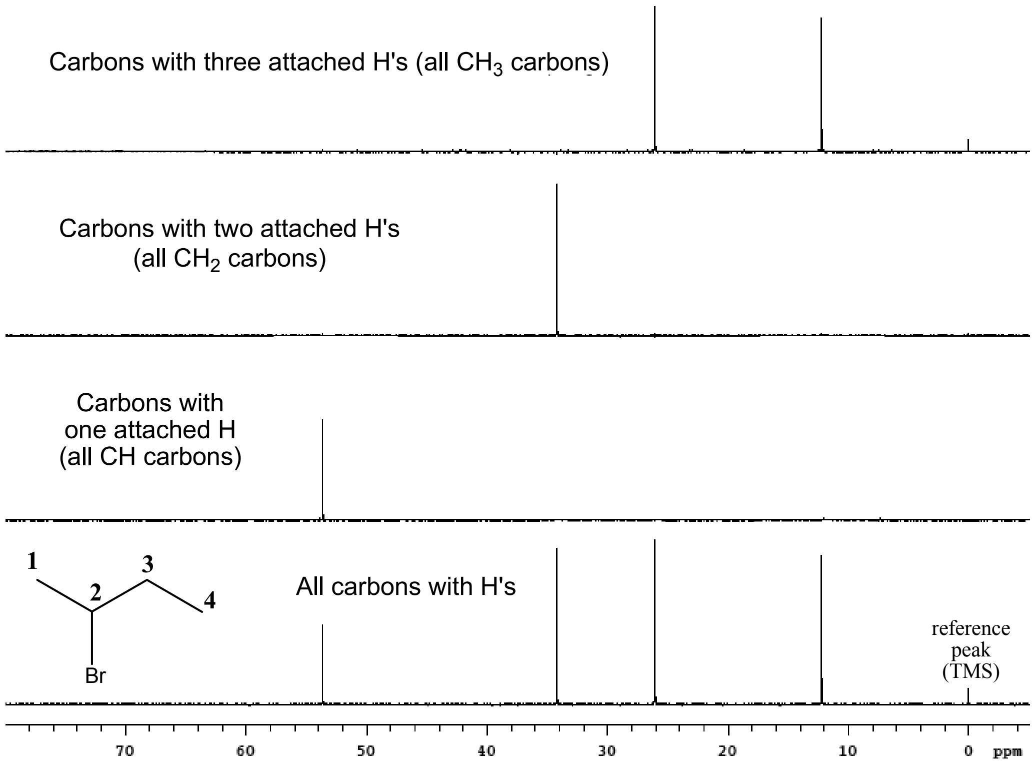


Figure L3.4: DEPT NMR Spectrum of 2-bromobutane

Critical Thinking Questions

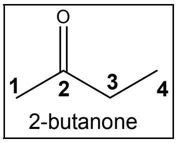
14. Even though each peak cluster on a DEPT spectrum appears as single peak, you can tell by the level on which it appears if it is a quartet, triplet, doublet, etc. Label each peak with the letter q, t, d, or s, and assign the peaks to carbons 1-4 on the structure of 2-bromobutane on the spectrum.

15. Look at the structure of TMS in Memorization Task L3.3 and explain why the TMS peak appears on the bottom and top levels of the DEPT spectrum.

Memorization Task L3.4: Singlets do not appear on a DEPT Spectrum

By convention, only carbons with H's appear on a DEPT spectrum. To see all the peaks including the singlet peaks you must look at an ordinary ^{13}C NMR spectrum.

16. Label each carbon on the structure of 2-butanone with a letter (s, d, t, or q) indicating the type of peak you expect for that carbon

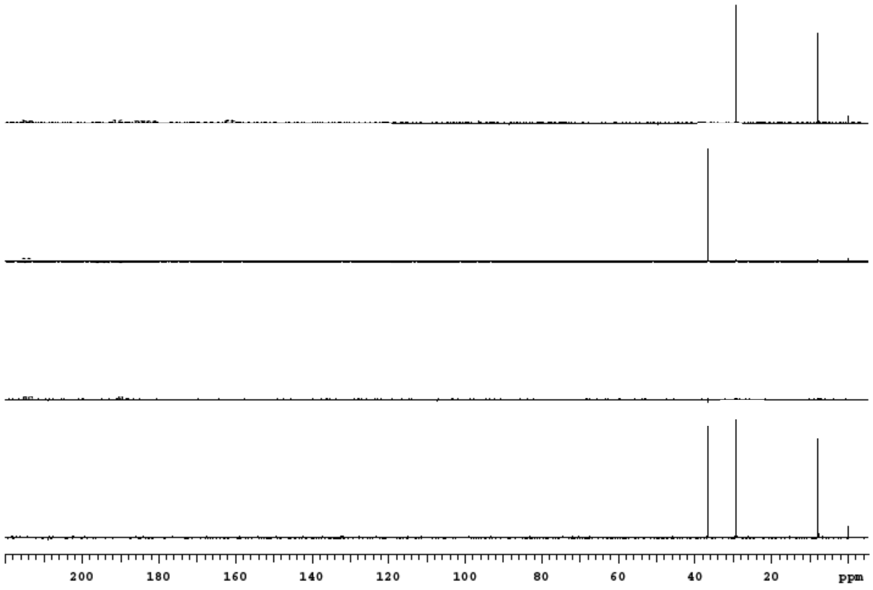


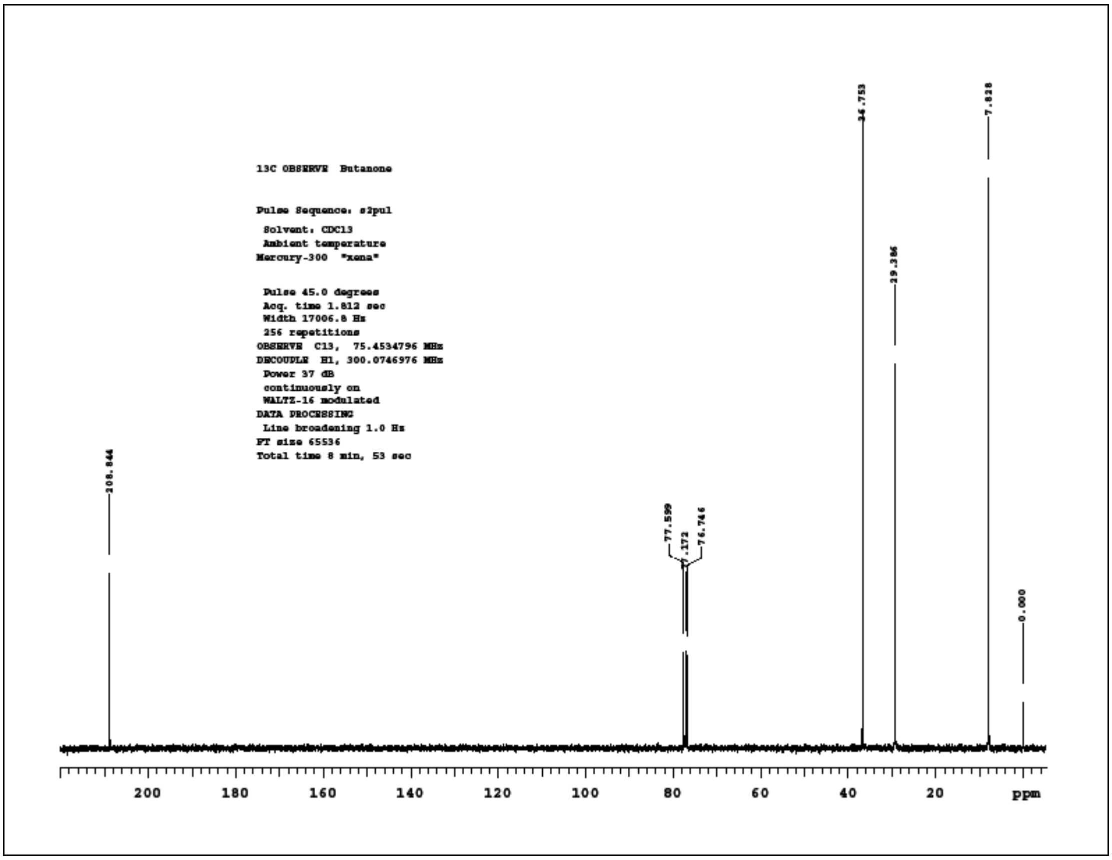
2-butanone

a. Label each peak on the DEPT spectrum of 2-butanone with a number (1, 2, 3, or 4) indicating its assignment to a specific carbon on the structure.

b. Which carbon of 2-butanone does not show up on the DEPT spectrum?

c. In what ppm range, and on what type of spectrum do you expect to find the peak for carbon 2? (Check your work: See Figure L3.5 on the next page.)





13C OBSERVE Butanone

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "xena"

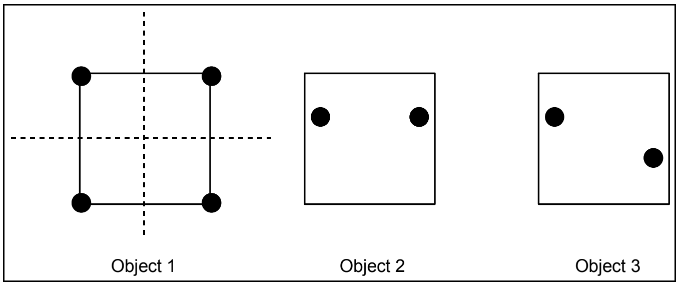
Pulse 45.0 degrees
Acq. time 1.812 sec
Width 17006.8 Hz
256 repetitions
OBSERVE C13, 75.4534796 MHz
DECOUPLE H1, 300.0746976 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 8 min, 53 sec

Figure L3.5: Ordinary ^{13}C NMR Spectrum of 2-butanone

Model 4: Symmetry Planes

Like all two-dimensional objects, Objects 1-3 have a plane of symmetry (also called a **mirror plane**) in the plane of the paper.

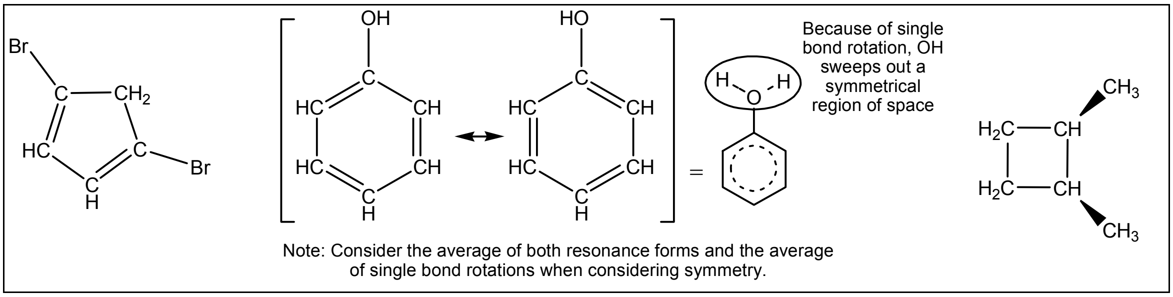
For Objects 1-3, some planes of symmetry are shown with dotted lines. Some are not.



Critical Thinking Questions

17. Mark the planes of symmetry that are NOT marked or noted in Model 4.
    a. Object 1 has two additional planes of symmetry. Mark them.
    b. Object 2 has one additional plane of symmetry? Mark it.
    c. Does Object 3 have any additional planes of symmetry? If so, mark them.

18. Mark each plane of symmetry in the following molecules.
(For each, indicate if the plane of the paper is a plane of symmetry by writing “POP”.)



Because of single bond rotation, OH sweeps out a symmetrical region of space

Note: Consider the average of both resonance forms and the average of single bond rotations when considering symmetry.

Model 5: Identifying Equivalent Carbons Using Symmetry

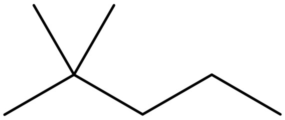
Two carbons are considered NMR (or chemically equivalent) if any of the following are true…

- They are directly across a mirror plane from one another.
- They can be rotated into one another without changing the overall representation of the molecule.

We will add one more item to this list later in the activity.

Critical Thinking Questions

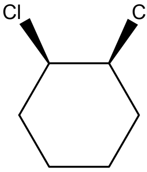
19. Make a model of 2,2,-dimethylpentane, and confirm that BOTH bullets in Model 5 are true for the three carbons attached to C_2. (Note that either bullet would be enough to make these three carbons equivalent and appear as one peak on a decoupled ^{13}C NMR spectrum).

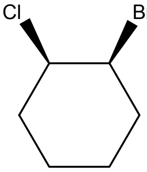


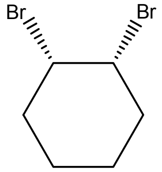
2,2-dimethylpentane

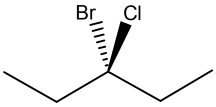
20. Number the carbons in each molecule in Figure L3.7 to show which ones are equivalent or distinct. That is, give equivalent carbons the same number. (When you number a molecule to assign its carbons to an NMR spectrum you do not have to follow IUPAC numbering rules.)

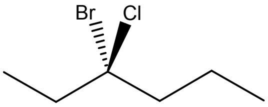
21. For the following molecules, confirm that the plane of the paper (POP) is NOT a symmetry plane.











a. Circle the two molecules that DO NOT contain any symmetry plane. For the others, mark all planes of symmetry using a dotted line.

b. Number the carbons to indicate which carbons are identical and which are distinct.

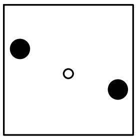
Check Your Work: Tips for finding symmetry planes in a molecule

Use the following tips to check your answers to the previous two CTQ's.

- If there are two of something (e.g., Br groups or methyl groups in Figure L3.7), look for a plane of symmetry halfway between them.
- If there is only one of something (e.g., OH group—see Figure L3.7), look for a plane of symmetry that contains that group.

Model 6: Rotational Symmetry Axis

Rotational symmetry axis = an axis around which the molecule as a whole can be rotated (some distance less than 360°) to result in an identical representation.



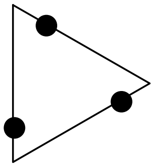
Object 3

Object 3 in Model 4 does NOT have any planes of symmetry (other than the plane of the paper). HOWEVER, it has a rotational symmetry axis. To test for this axis, put your pencil on the open dot ◦ and spin the paper until the object looks exactly as it did at the start. **YOUR PENCIL DEFINES THE ROTATIONAL SYMMETRY AXIS.**

Critical Thinking Questions

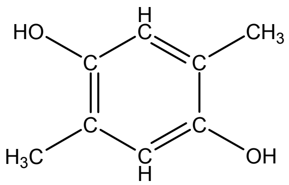
22. Rotating Object 3 _______ degrees (number less than 360) results in an identical representation.

23. Consider the object at right.



   a. Mark the rotational symmetry axis with a ◦
   b. What is the minimum angle you can rotate this object to give an identical representation?

24. Carbons that can be rotated into one another via a rotational symmetry axis are NMR equivalent and chemically equivalent.



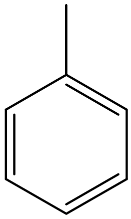
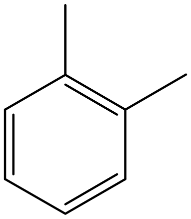
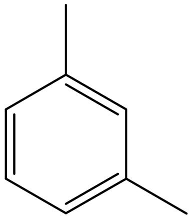
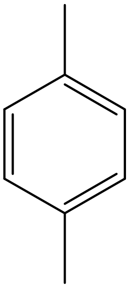
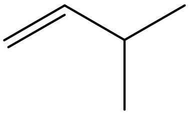
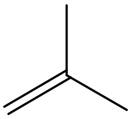
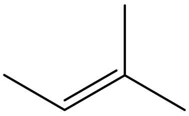
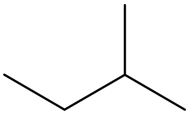
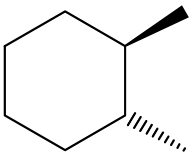
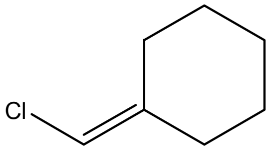
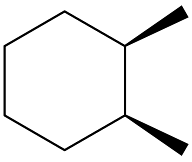
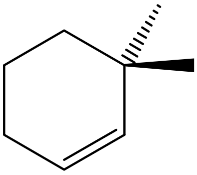
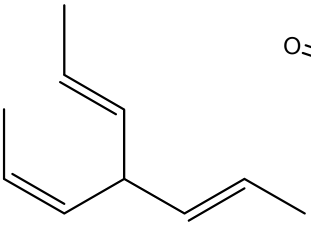
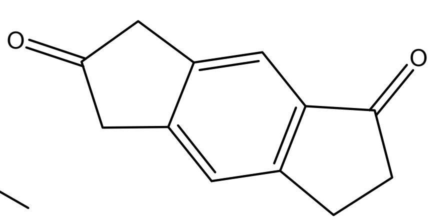
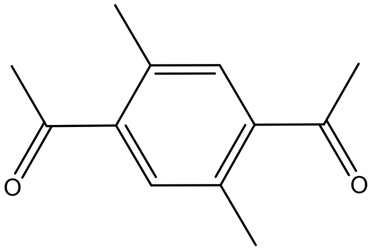
   a. Make this rule a third bullet in Model 5.
   b. Does the molecule at right have any plane of symmetry (other than the plane of the paper)? If so, mark it with a dotted line.
   c. In this case, does the plane of symmetry in the plane of the paper cause any carbons to be equivalent to each other? If so, which ones?
   d. Does this molecule have a rotational symmetry axis? If so, mark it with a ◦.
   e. Number the carbons to indicate which are identical and which are distinct.

Exercises

1. Often a symmetry plane is coincident with a rotation symmetry axis. Which two dotted lines that you drew in Figure L3.7 (to represent mirror planes) are also rotation symmetry axes?

2. Draw a representation of 3,3-dimethylhexane so that its symmetry plane is in the plane of the paper.
   a. Circle the two identical carbons on this molecule.
   b. True or False: A symmetry plane in the plane of the paper cannot be used to show that two carbons are identical. If true show this plane for 3,3-dimethylhexane.

3. For each structure:
   a. Find each mirror plane and each rotation axis.
   b. Number the carbons, giving the same number to equivalent carbons.
   c. Label each carbon with a letter to indicate the multiplicity of its ^{13}C NMR peak (s, d, t, or q), and where it would appear on a DEPT spectrum.

4. Complete the sentence: In coupled ^{13}C NMR, the number of peaks in a peak cluster ("multiplicity of the peak cluster") tells you…

5. Complete the sentence: In ^{13}C NMR, the location of the peak cluster along the x axis (ppm value) tells you…

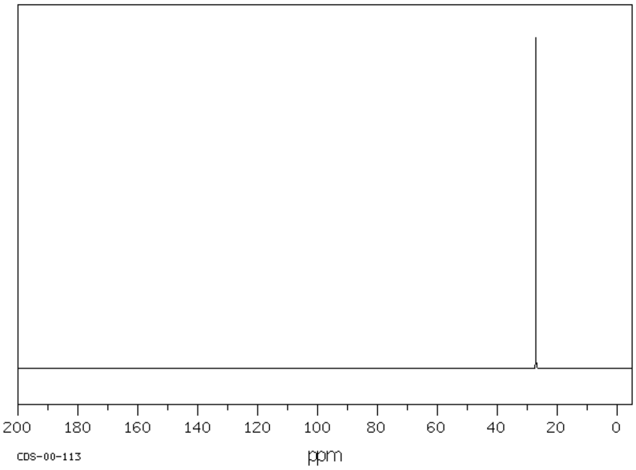
6. Complete the sentence: In decoupled ^{13}C NMR, the number of peaks tells you…

7. Complete the sentence: In decoupled ^{13}C NMR, the height of a peak tells you…

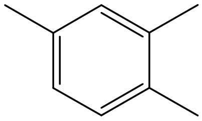
8. Chemists rarely use proton-coupled ^{13}C NMR spectra. Explain why.

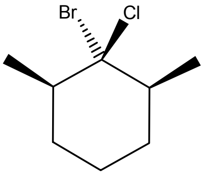
9. **T** or **F**: In decoupled ^{13}C NMR each peak cluster is reduced to a singlet (a single peak).

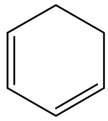
10. The decoupled ^{13}C NMR spectrum of a molecule with the molecular formula C_6H_{12} is shown at right. On the basis of this spectrum, propose a structure for this molecule.

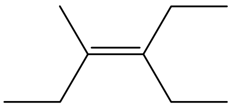


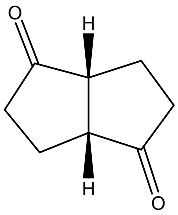
11. For each structure:
    - Number the carbons, giving the same number to equivalent carbons.
    - Label each carbon with a letter to indicate the multiplicity of its ^{13}C NMR peak (s, d, t, or q), as it would appear on a coupled CMR spectrum.





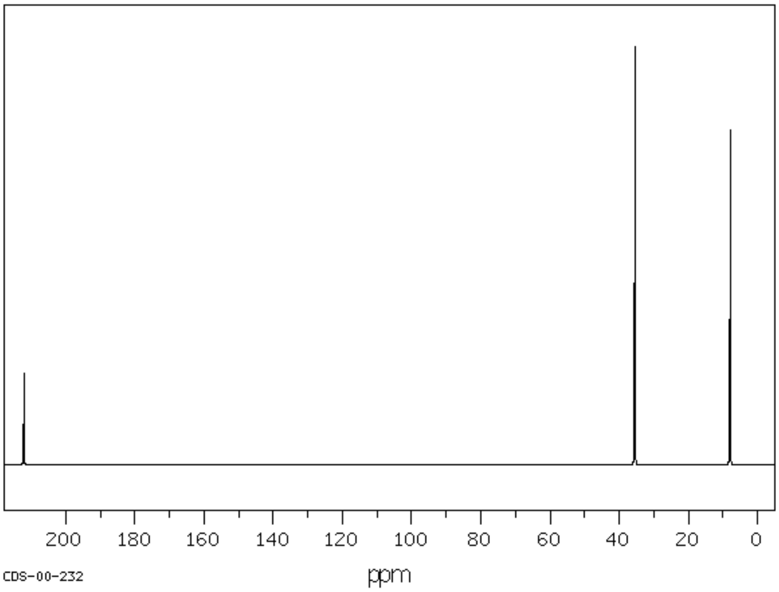




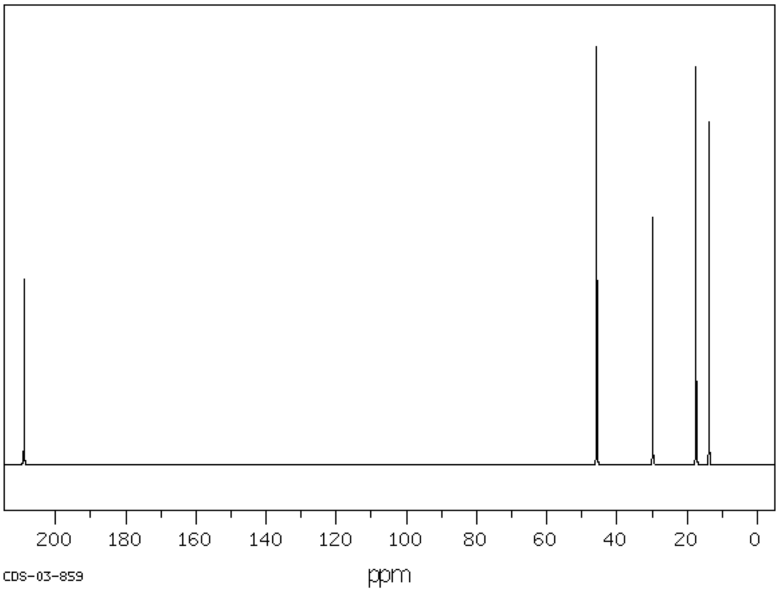


12. Draw the structure of the molecule with molecular formula $C_6H_6O_2$ that is expected to have only the following two carbon NMR peaks: 140.6 ppm, s; and 117.8 ppm, d.

13. Below is the CMR spectrum of a molecule with molecular formula $C_5H_{10}O$. Draw a likely structure of the molecule. The DEPT shows the peaks (from left to right) to be: s, t, q.



14. The following is a CMR of an isomer of the compound above. Draw a possible structure.



15. Read the assigned pages in the text, and do the assigned problems.

The Big Picture

NMR (nuclear magnetic resonance) spectroscopy is the most powerful tool that scientists have for looking at the structure of organic molecules. Medicine makes extensive use of this technique–though they drop the word "nuclear" and call it MRI (magnetic resonance imaging). The physics behind NMR is very complex, although it is, at its root, similar to IR—except that radio frequency light is used instead of infrared light. The very-low-energy radio waves excite a property called **nuclear spin**. Though this physics is very interesting, there is little need for most organic chemists to understand the theory and physics behind NMR. **It is critical, however, that an organic chemist be an expert at interpreting NMR spectra**. Therefore, this is the focus of the activity and the next.

This activity covers carbon NMR. Each peak in a (decoupled) carbon NMR spectrum is due to a unique carbon on the analyte molecule. The next activity covers hydrogen NMR (also called ^{1}H NMR, proton NMR or PMR). In proton NMR, each peak is due to a unique **hydrogen** in the molecule.

Organic chemists use the powerful combination of carbon NMR, proton NMR, and MS to deduce the structure of most unknown molecules.

Common Points of Confusion

- **ppm** or **chemical shift**: If a C is close to an electronegative element or involved in a multiple bond, or both, you will find the corresponding peak at higher ppm (farther left on the spectrum). Each chemically distinct C should have a unique chemical shift, though in practice different peak clusters sometimes overlap just by coincidence. This can make interpretation of coupled spectra very difficult. This is why decoupled spectra are usually taken.

- **Peak height/area** has LITTLE MEANING in C-13 NMR. Peak area is a function of many things, one being whether the C is 1°, 2°, 3°, or 4°. It is difficult to interpret the meaning of peak height in C-13 NMR.

- **Multiplicity** in a proton-coupled ^{13}C NMR spectrum tells you the number of H's attached to a given carbon. For example, a C that produces a doublet (two peaks) must have exactly one H attached to it. Very often chemists record "proton-decoupled" ^{13}C NMR spectra. Such spectra have a singlet for each chemically unique carbon. This is useful for complex molecules for which the peak clusters would overlap. A decoupled ^{13}C NMR spectrum tells you the number of different carbon atoms present in the sample, but not the multiplicity. This is where a DEPT spectrum can be very useful as it tells you the multiplicity of each peak appearing on the ^{13}C NMR spectrum.

- **DEPT** spectra do not include singlets. This means it is usually necessary to use a DEPT in conjuction with an ordinary ^{13}C NMR spectum. Using the DEPT, you can assign each peak on the ordinary ^{13}C NMR spectum as a siglet, doublet, triplet, or quartet.

- For the purpose of determining symmetry, group such as OH are considered highly symmetrical due to single bond rotation, even though, when you draw them they look like they break the symmetry of the molecule.

- The difference between bullet number two in Model 5 (The carbons can be rotated into one another without changing the overall representation of the molecule.)and a rotational symmetry axis is subtle. For bullet two in Model 5 to hold true you need only rotate one bond. For example, this rule explains why the three carbons of a *tert*-butyl group are equivalent. In contrast, if a molecule contains a rotational **symmetry axis** this means the WHOLE MOLECULE can be rotated on this axis some distance (e.g. 180) such that the result looks the same as the starting position.

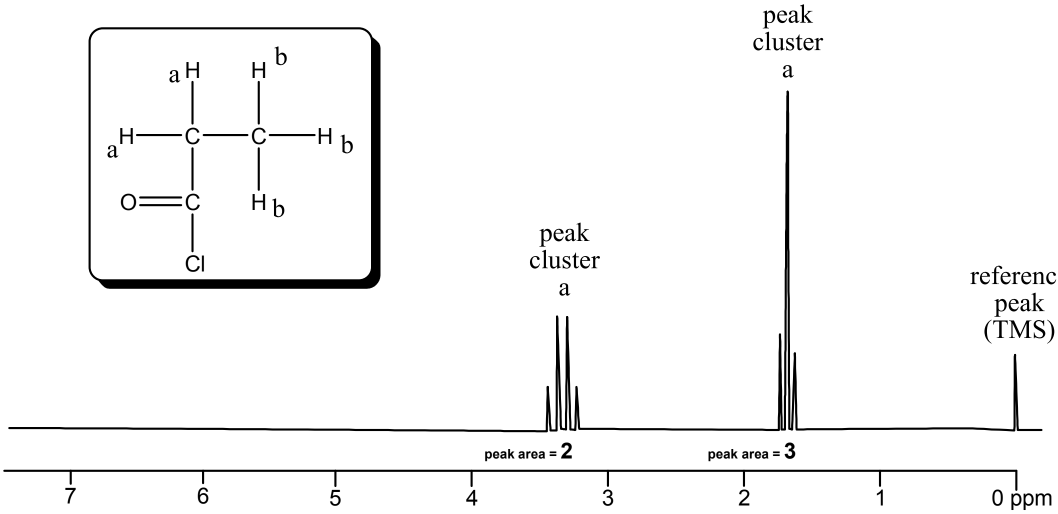
ChemActivity L4: Proton (^1H) NMR Spectroscopy

(What can a ^1H NMR spectrum tell you about the structure of a molecule?)

This activity is designed to be completed in a 1 ½ hour laboratory session or two classroom sessions.

Model 1: Carbon NMR versus Hydrogen NMR ("Proton NMR")

In ^{13}C NMR the signals are generated by carbon nuclei. ^1H NMR signals are generated by **hydrogen nuclei.** Most ^1H NMR peaks appear between 0–12 ppm. ^{13}C NMR peaks appear between 0–220 ppm.



The peak at 0 ppm is a **reference peak** associated with the additive **TMS**, not the molecule in the box.

Critical Thinking Questions

1. (E) How many different types of chemically distinct H's are there on the structure in Model 1?
2. (E) How many peak clusters are there on the spectrum in Model 1?
3. (E) Complete the following sentence: In a proton NMR spectrum there is one peak cluster for each chemically distinct type of **H** or **C** [circle one].
4. The number listed below a peak cluster gives you the **area of the peak cluster**. **Peak cluster area** is a measure of the size of the peak cluster.
   a. (E) Which peak cluster **a** or **b** [circle one] is bigger (as measured by area)?
   b. (E) What is the ratio of the size of peak cluster a : size of peak cluster b?
   c. (E) How many H's are there of **type a**? … **type b**? Does this match the ratio above?
   d. Hypothesize: What structural information is conveyed by peak cluster areas in ^1H NMR?

   e. Construct an explanation for why **peak cluster area**, and not peak height, is used to determine the number of H's associated with a peak cluster. (Hint: Can you imagine a tall thin peak cluster with a smaller area than a shorter, but broader peak cluster?)

Memorization Task L4.1: Peak area tells you number of H's associated with peak cluster

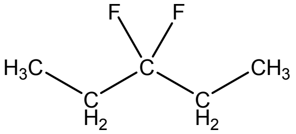
Peak area is calculated (by the instrument) using a mathematical technique called **integration**. For this reason **peak cluster area** is often referred to as a peak's **integral**, **integration**, or **integrated area**.

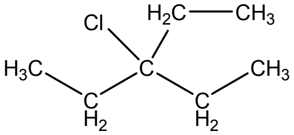
The area of each peak cluster is often represented by a number written above or below a peak cluster.

This integration number tells you the relative number of H's associated with each peak cluster. Because it is a *relative* number, the ratio 2:3 would also apply to a molecule with [4 & 6 H's] or [6 & 9 H's], etc.

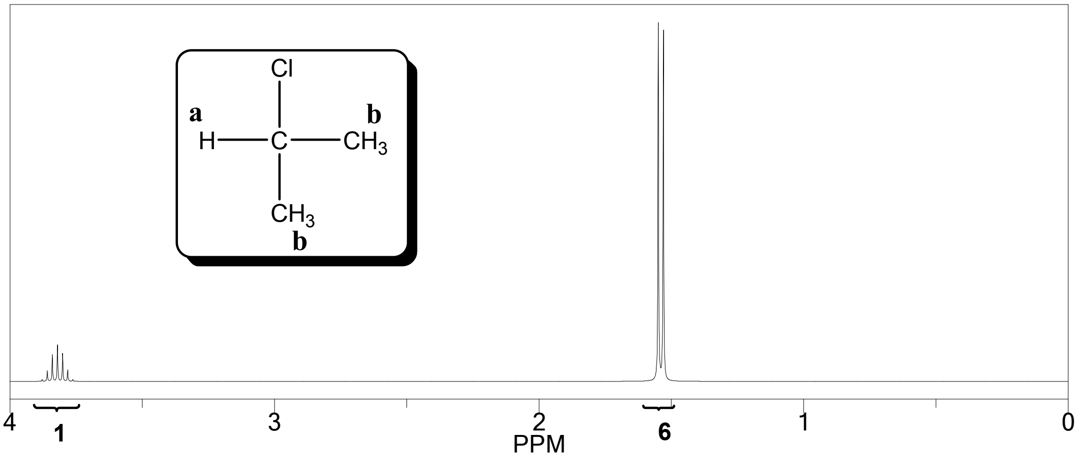
Be careful! Peak area (not peak height) tells you the number of H's associated with a peak cluster. That is, sometimes a tall, thin peak will have a smaller area than a short, broad peak.

5. Explain why the integration ratio on a proton NMR spectrum of *either* of the following molecules is 2:3. (The same as the ratio for the molecule in Model 1.)



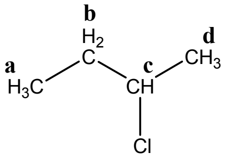


6. **For now, don't worry about the number of peaks in a peak cluster. We will deal with that on the next page.** Based only on the integration of each peak cluster (shown as a bold number below the cluster) assign a letter to each peak cluster matching it to the correct type of H on the structure.



7. a. Construct an explanation for why three H's attached to the same carbon (a methyl group) are equivalent (for example, see the structures above and below).

   b. Construct an explanation for why the two CH_3 groups on the structure above are equivalent (making all 6 H's labeled "**b**" equivalent), but the two CH_3 groups on the structure at right are NOT equivalent.



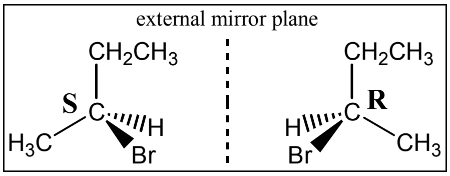
Memorization Task L4.2: Finding NMR Equivalent H's using Symmetry

Our rules for finding equivalent carbons also apply to finding equivalent hydrogens. These rules state that two hydrogens are equivalent if any of the following hold true. The hydrogens…

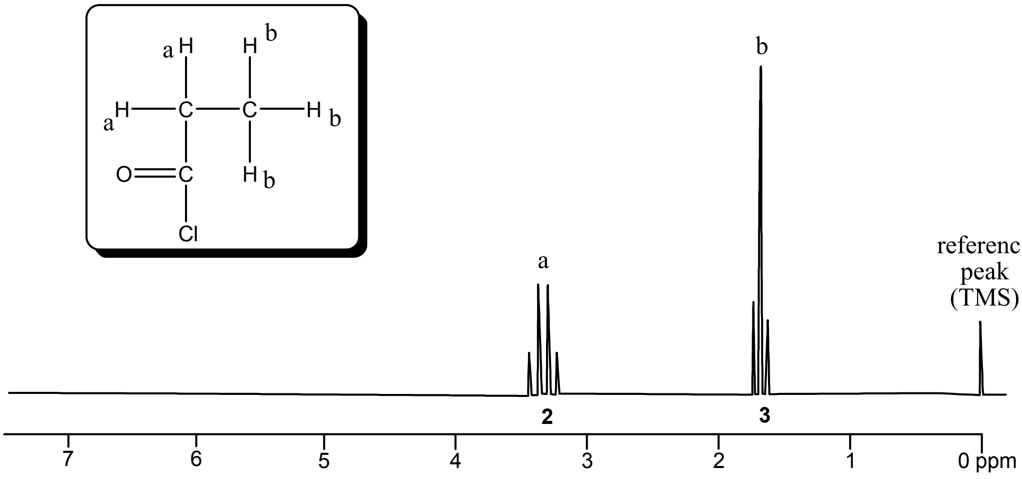
- are directly across a **mirror plane** (**symmetry plane**) from one another.
- can be rotated into one another without changing the overall representation of the molecule.
- can be rotated into one another via a rotational **symmetry axis**.

For those who have completed ChemActivity 12…

Interestingly, it turns out that H's on different molecules are NMR equivalent if there is an external mirror plane that links them. This means that **a molecule and its enantiomer will produce the exact same NMR spectrum**. That is, enantiomers are indistinguishable from one another by NMR.



8. The spectrum from Model 1 is reproduced below. Recall that a cluster with one peak is called a singlet, two peaks = doublet, three peaks = triplet, and four peaks = quartet. Any cluster with five or more peaks will be called a multiplet. Label peak clusters a and b, below, with singlet (s), doublet (d), triplet (t), quartet (q), or multiplet (m), as appropriate



9. Look back at Memorization Task L3.1 in the previous ChemActivity. Recall that in ^{13}C NMR one attached hydrogen could split an NMR peak into a doublet, two attached hydrogens could split it into a triplet, etc.. By counting peaks in a cluster you could determine the number of hydrogens attached to a given carbon. It turns out that in ^{1}H NMR counting peaks in a cluster tells you the **number of nearest neighbor hydrogens that are not equivalent**. For the spectrum above…
   a. (E) How many times was **peak cluster a** "split/cut" to product the **four** peaks shown?
   b. Identify the **three** neighboring H's on the structure which split **cluster a** into four peaks?

   c. (E) How many times was **peak cluster b** "split/cut" to product the **three** peaks shown?
   d. Identify the **two** neighboring H's on the structure which split **cluster b** into three peaks?

Memorization Task L4.3: Multiplicity tells you the number of "foreign" H's within 3 bonds

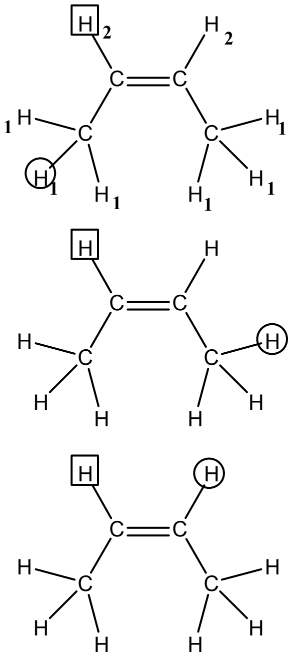
In ^1H NMR, H's split the signals of foreign (= non-equivalent) hydrogens within three bonds.

This means **chemically equivalent H's DO NOT split each other**.

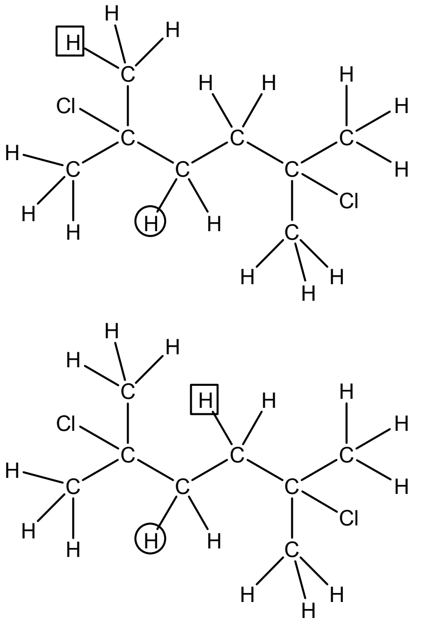
(Review) In ^{13}C NMR, H's split the signal of carbons one bond away.

10. Confirm that Memorization Task L4.3 explains the splitting patterns of the spectra in CTQ's 6 & 8.

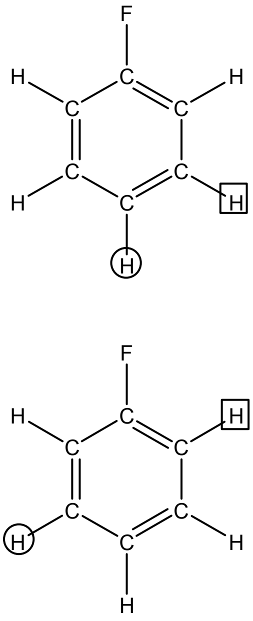
11. For each individual drawing, indicate whether the circled H will split the signal of the boxed H. (When counting bonds for splitting, ignore whether a bond is a single, double, or triple bond. For example, the circled and boxed H's in the first column are 3, 4, and 3 bonds apart, respectively.)



Molecule I



Molecule II



Molecule III

12. On the first row of structures above…

    a. Label each hydrogen on the structure with a number, giving identical hydrogens the same number. (The first one is done for you.)

    b. For molecules II and III, complete a table, like the one for Molecule I, below, by reporting the **integration** and **multiplicity** of the peak due to each type of hydrogen.

Molecule I	Integration	Multiplicity
H_1	6*	d
H_2	2*	q

*Ratio of H_1 to H_2 could also be reported as 3:1

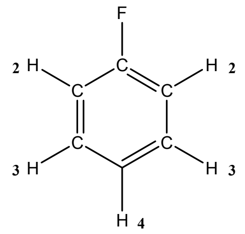
13. (Check your work) Explain why, for Molecule II, the H's on carbons 3 and 4 do not split one another even though they are only three bonds apart.

14. (Check your work) There are no CH_2 (methylene) groups on Molecule III, yet the signal due to the H on carbon 4 is a triplet. Explain how a triplet can occur with no CH_2 group next door.

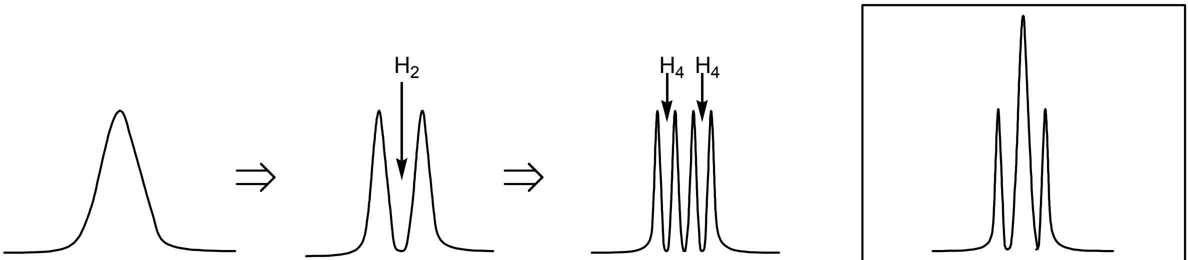
Model 2: Doublet of Doublets versus Triplet

If H_2 and H_4 are similar, the peak due to H_3 will be a triplet. If not, a different cluster called a doublet of doublets can occur.

The cartoon below illustrates how, depending on spacing, either a **doublet of doublets** or a **triplet** will be found for H_3.



Molecule III



peak due to H_3 before any splitting

H_2 splits this peak into a doublet.

H_4 splits each of these peaks, producing a **doublet of doublets**

if middle two peaks are pushed together, it looks like a **triplet**

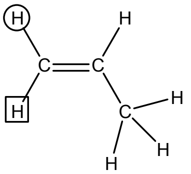
Critical Thinking Questions

15. (E) Confirm that each H_3 in Molecule III is split by both an H_2 and H_4

16. (E) Confirm that H_2 in Molecule III is NOT equivalent to H_4

17. (E) Explain why H_3 in Molecule III could appear as a doublet of doublets.

18. Two H's attached to the *same carbon* (in rare cases) can be inequivalent. Construct an explanation for why the circled H on the structure at right is NOT chemically equivalent to the boxed H. *(See the next question for a hint.)*



a. *(Hint for above)* Is the circled H *cis* or *trans* to the methyl group? What about the boxed H?

b. Label each H on the structure above with a number, giving identical H's the same number.

Memorization Task L4.4: Doublet of Doublets

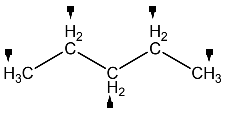
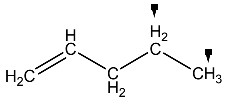
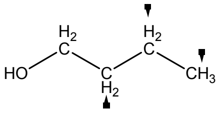
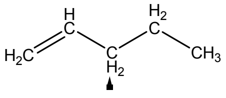
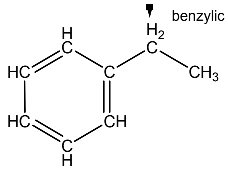
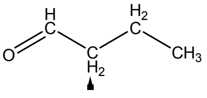
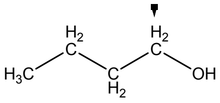
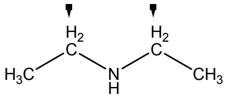
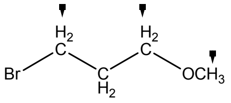
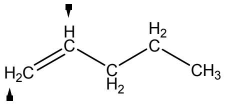
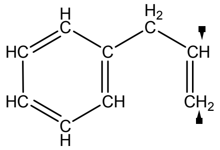
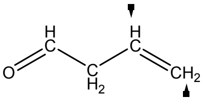
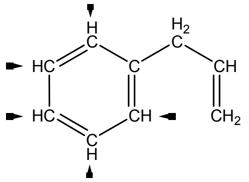
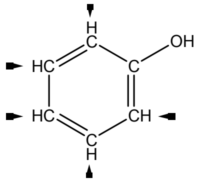
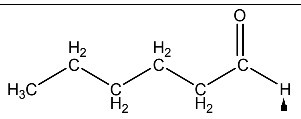
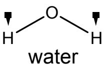
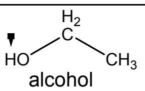
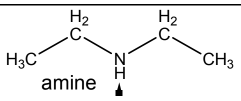
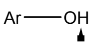
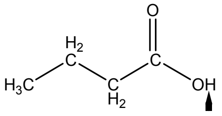
When exactly two **in**equivalent H's split a given H, report the multiplicity as "**dd**" for **doublet of doublets (dd)**.

c. Fill in the table reporting the multiplicity and integration of the peak due to each type of hydrogen.

propene	Integration	Multiplicity
H_1		
H_2		
H_3		
H_4		

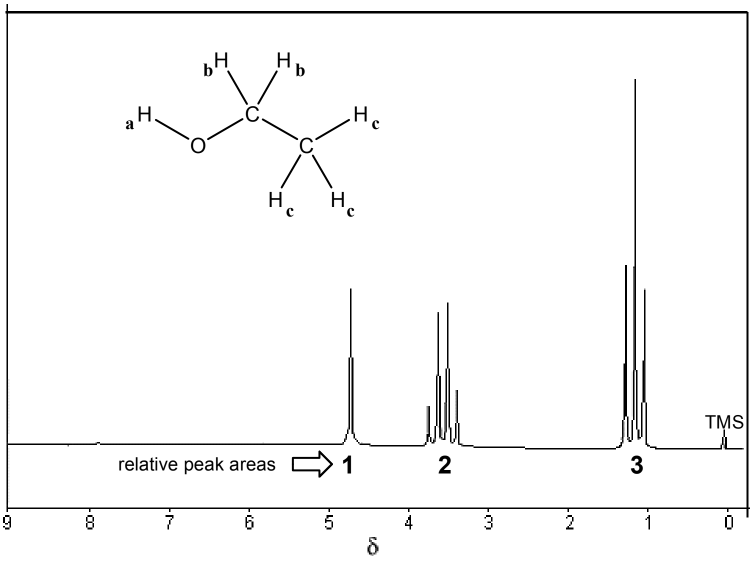
19. On a proton NMR spectrum, the chemical shift (ppm/placement along the x axis) conveys similar information as in ^{13}C NMR. Explain why **peak cluster a** is farther to the left (higher ppm) than **peak cluster b** on the spectrum in Model 1.

Memorization Task L4.5: Memorize the following ^{1}H NMR Chemical Shifts (ppm ranges)

Type of Carbon	Examples Marked H's are within the given **NMR ppm ranges (^{1}H)**	ppm Range
H three or more bonds from a functional group	  	1 - 2
H two bonds from π bond (C=C or C=O)	 allylic  benzylic  "alpha" to a carbonyl	2 – 3 (1.8-2.6)
H two bonds from O, N, or halogen	  	3 – 4 (2.5-4.5)
H attached to C=C (not benzene)	  	4 – 7 (4.5-7)
H attached to benzene ring	 	7 – 9 (6.5-8.5)
H attached to carbon of C=O (carbonyl)		10 (9.7-10)
H attached to O or N	 water  alcohol  amine  phenol	1 - 8
	carboxylic acid 	10 - 13

Critical Thinking Questions

20. Alcohols do not always follow the rules for predicting multiplicities. Based on integration and chemical shift alone, assign each of the three (non-reference) peaks in the proton NMR of ethanol at right.



21. Write the expected multiplicity above each peak cluster associated with ethanol. Which clusters in the spectrum above have a multiplicity that does not fit the rules we have learned so far?

Memorization Task L4.6: An H attached to N or O usually does not participate in splitting.

22. Illustrate how Memorization Task L4.6 explains the inconsistencies you noted above.

Model 3: Proton NMR of H's attached to N or O

An H attached to N or O often appears as a broad singlet on a proton NMR spectrum. This is true even if the H is within three bonds of a foreign H (as is the case with ethanol). Also watch out for the fact that the integration of an H attached to O or N can be inaccurate.

These irregularities are attributable to hydrogen bonding between sample molecules and the small amount of water present in all samples prepared in air. (There is a significant amount of water in air).

Not only do H's on O or N hydrogen bond to water, they actually exchange with H's on water.

Critical Thinking Question

23. Construct an explanation for why the peak at 4.8 ppm in the spectrum at the top of the page disappears completely if a second NMR is taken a few minutes after adding a drop of D_2O to the NMR sample. (Note that deuterium does not show up on a proton NMR spectrum.)

Memorization Task L4.7: Deuterium Exchange

D_2O can be added to a NMR sample to determine which peaks are due to an H attached to an O or N.

Model 4: NMR Solvents

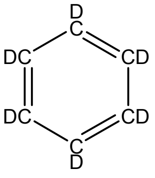
Typically, a solvent is present in much higher concentrations than the molecule being analyzed. This means NMR solvents must not have any hydrogens. If an NMR solvent has even one hydrogen, the huge solvent peak will obscure all the peaks of the analyte molecule.

$CDCl_3$ (deuterated chloroform, or chloroform-d) is the most common NMR solvent because it is cheap relative to other deuterated solvents, dissolves most organic molecules, and has no hydrogens.

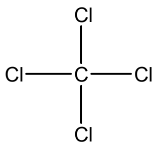
Most $CDCl_3$ is contaminated with a very tiny amount of $CHCl_3$. This turns out to be a good thing since the tiny $CHCl_3$ peak (which appears at 7.24 ppm) can be used as a reference peak instead of adding TMS.

Critical Thinking Questions

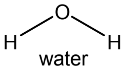
24. Cross out the two molecules below that cannot serve as a proton NMR solvent.



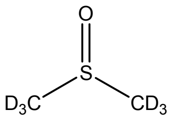
benzene-d_6



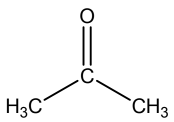
carbon tetrachloride



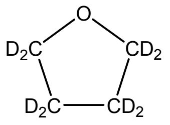
water



DMSO-d_6

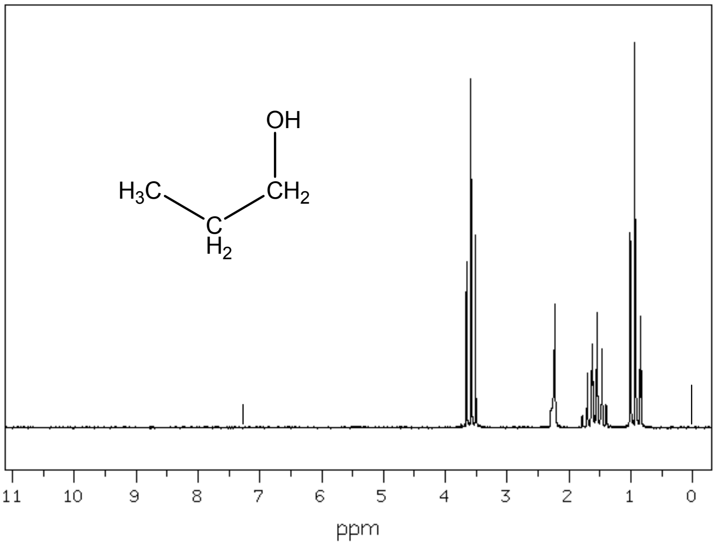


acetone



THF-d_8

25. Identify/assign each peak (including any solvent or reference peaks) on the following spectrum.

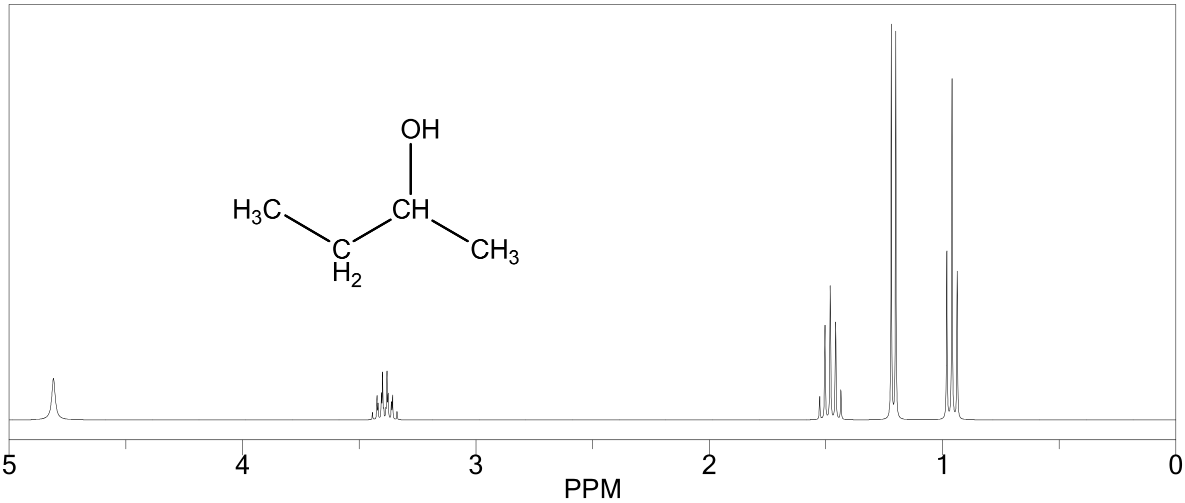


26. Above each peak cluster due to 1-propanol, write the expected integration value.

27. (Check your work) Are your assignments above consistent with the fact that only the peak at 2.23 ppm disappears when the sample is treated with D_2O (**deuterium exchange**)? Explain.

Exercises

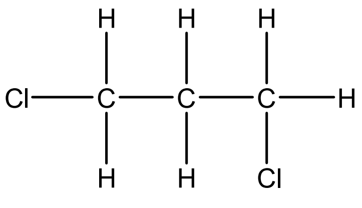
1. Assign each peak on the following spectrum.

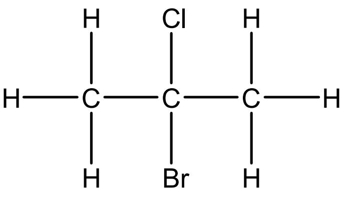


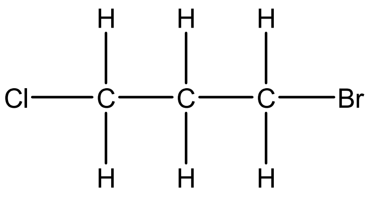
2. Predict the integration value associated with each peak cluster on the spectrum above.

3. Here are proton NMR data for 1-bromopropane: H_a: triplet (2H) 3.32ppm; H_b: multiplet (2H) 1.81ppm; H_c: triplet (3H) 0.93ppm. (Relative integrations shown in parentheses.)
   a. Through how many bonds can a hydrogen split another hydrogen?
   b. According to this splitting rule, does H_a split H_c?
   c. Is your answer in part a) consistent with the multiplicity listed for peak clusters a and c?
   d. How many hydrogens split H_b?
   e. Upon very close inspection of the proton NMR spectrum of 1-bromopropane, you would find that peak cluster b has at least six peaks. Is this consistent with your answer in part d)?
   f. Speculate as to why any peak cluster with more than four peaks is listed simply as a "multiplet."

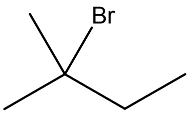
4. For each structure below, use letters or numbers to indicate chemically equivalent and distinct hydrogens, and make a table showing the predicted integration and multiplicity of each peak cluster.

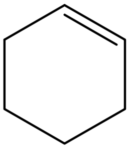


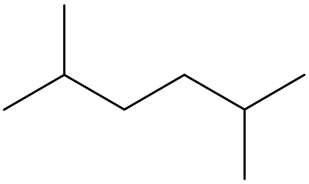


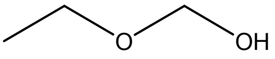


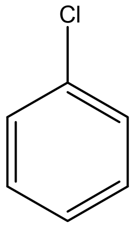
5. For each structure below, use numbers to indicate chemically equivalent and distinct hydrogens, and make a table showing the predicted integration and multiplicity of each peak cluster.

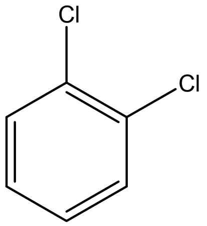


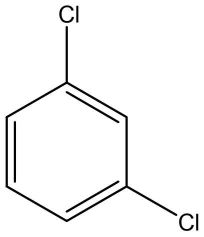


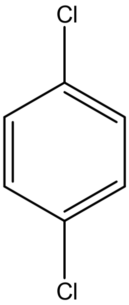


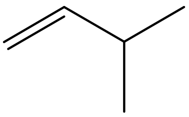


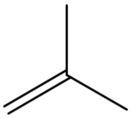


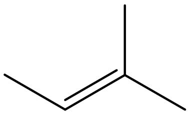


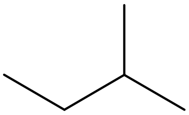


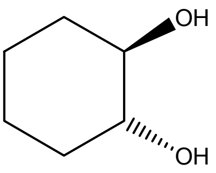


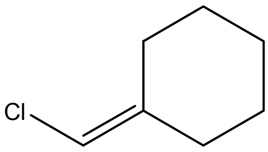


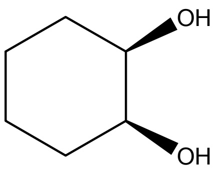


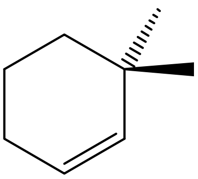


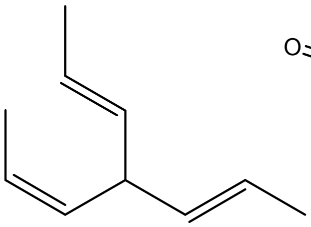


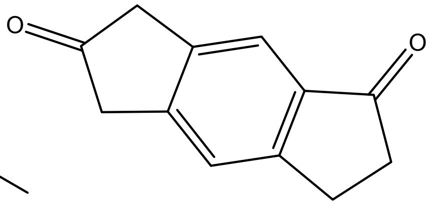


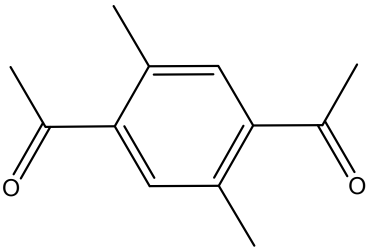








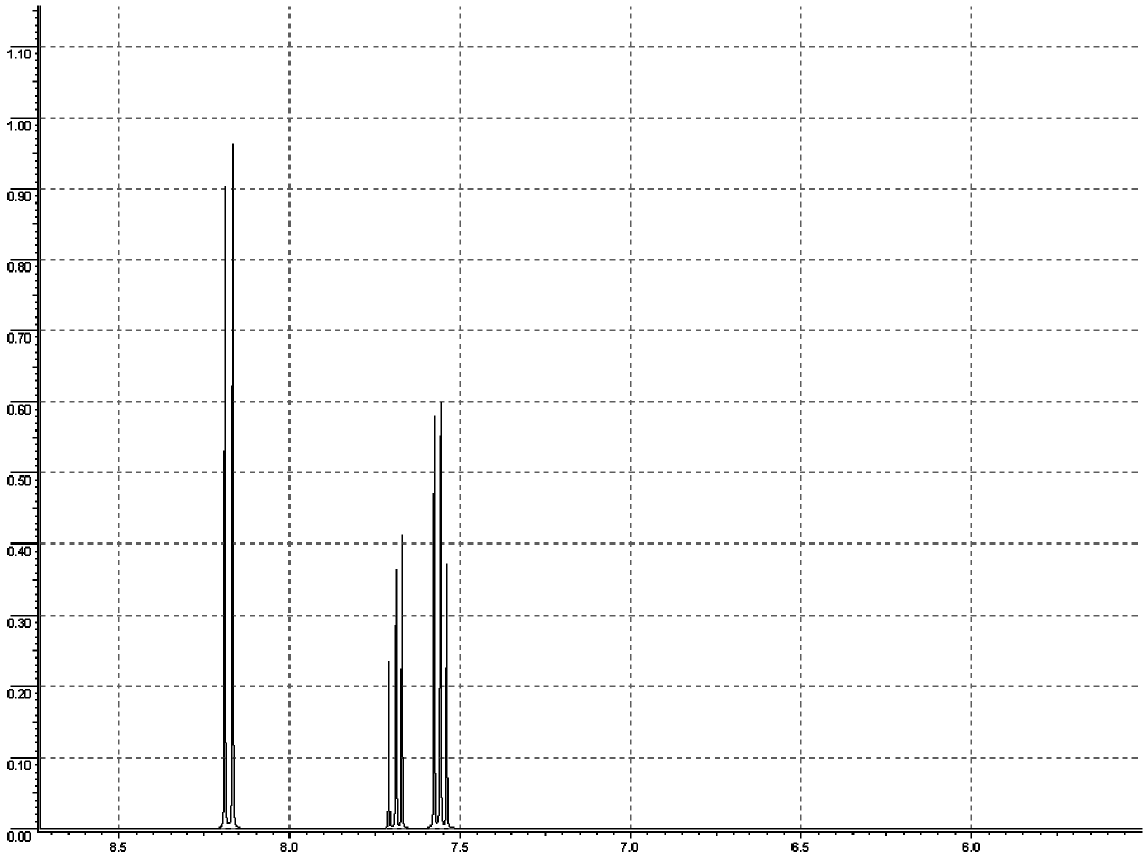




6. (*If you have completed ChemActivity 12…*) Imagine you have two bottles: one with (R) and the other with (S)-2-bromobutane. Unfortunately, your lab partner messed up and labeled both bottles simply "2-bromobutane." Can you use NMR to sort out this problem? Explain why or why not.

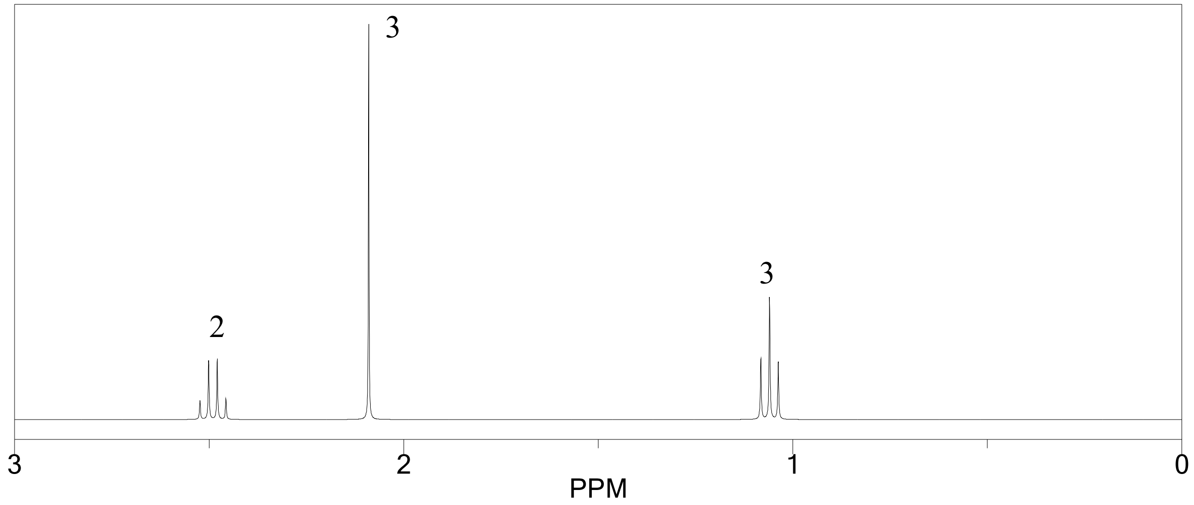
7. A researcher wants to take a proton NMR of a molecule that dissolves only in water. What solvent should she use to make the NMR sample?

8. Based on the ppm range in which the peaks appear on the spectrum below, what can you infer about the molecule associated with the spectrum?



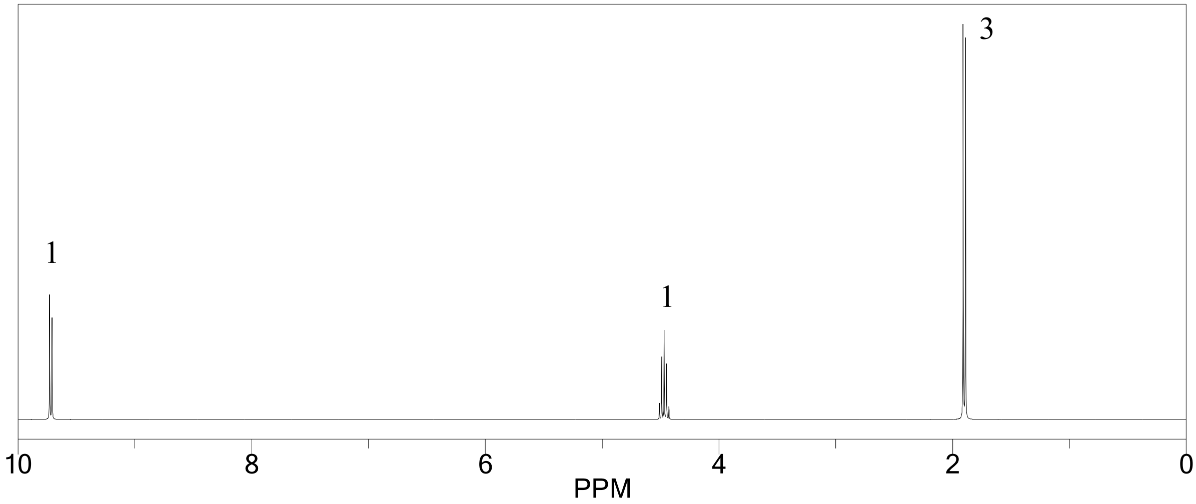
9. Propose a structure to go with the spectrum above assuming the unknown has molecular formula $C_6H_5NO_2$, and the integrations of the peaks are 2:1:2, from left to right.

10. Propose a structure to go with the spectrum below assuming the unknown has molecular formula C_4H_8O, and the integrations are as shown. (*Hint*: First determine the degrees of unsaturation.)



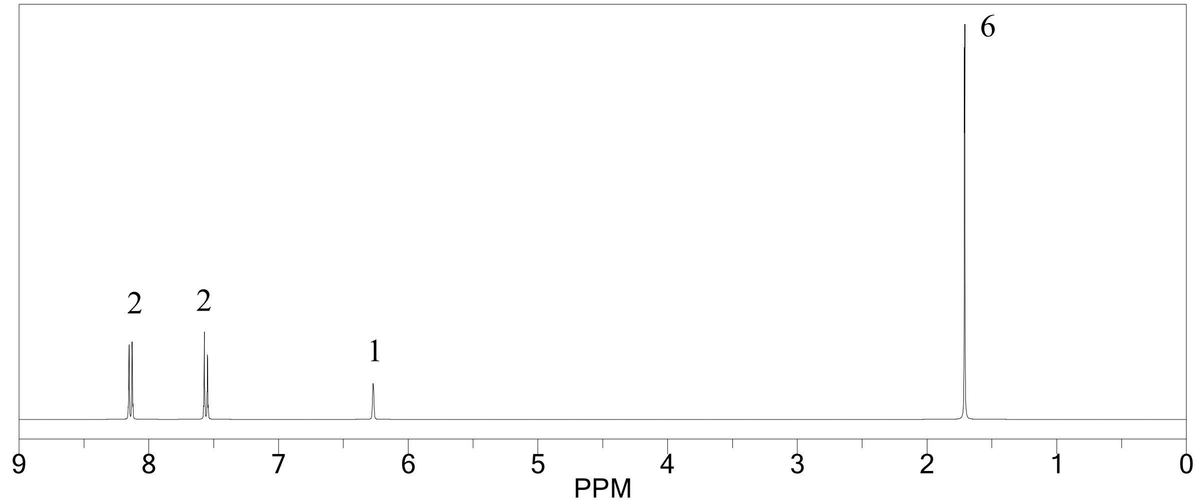
11. (Check your work) The peaks at 1.1 and 2.5 ppm on the previous page represent the signature pattern of an ethyl group. This pattern (a quartet worth 2H's and a triplet worth 3 H's) is so common it is worth memorizing.
    a. Find this pattern on the proton NMR spectrum of ethanol in CTQ 20.
    b. Sketch the proton NMR spectrum expected for diethyl ether ($CH_3CH_2OCH_2CH_3$).

12. Propose a structure to go with the proton NMR spectrum and the following mass spectral data: $[M]^+ = 136$ (100), $[M+1]^+ = 137$ (3.3), $[M+2]^+ = 138$ (97.3)



13. Construct an explanation for why the peak in the spectrum above found at 4.5 ppm is outside the typical range for a hydrogen alpha to a carbonyl (2-3) *and* the typical range for a hydrogen bound to the same carbon as a halogen (3-4).

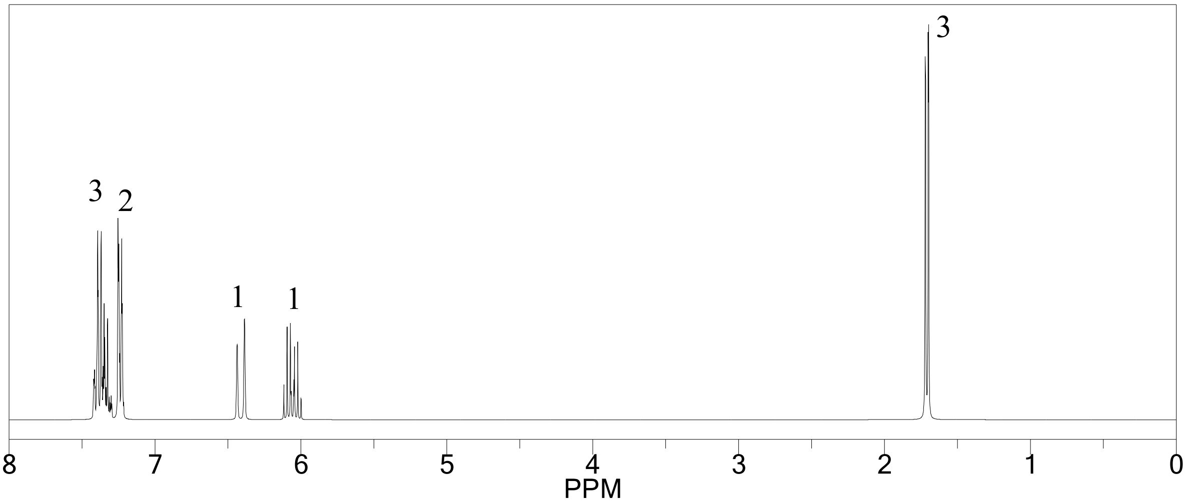
14. Draw the structure of an unknown to go with this proton NMR and the following mass spectral data: $[M]^+ = 166$ (50), $[M+1]^+ = 167$ (5.5), $[M+2]^+ = 168$ (16.1)

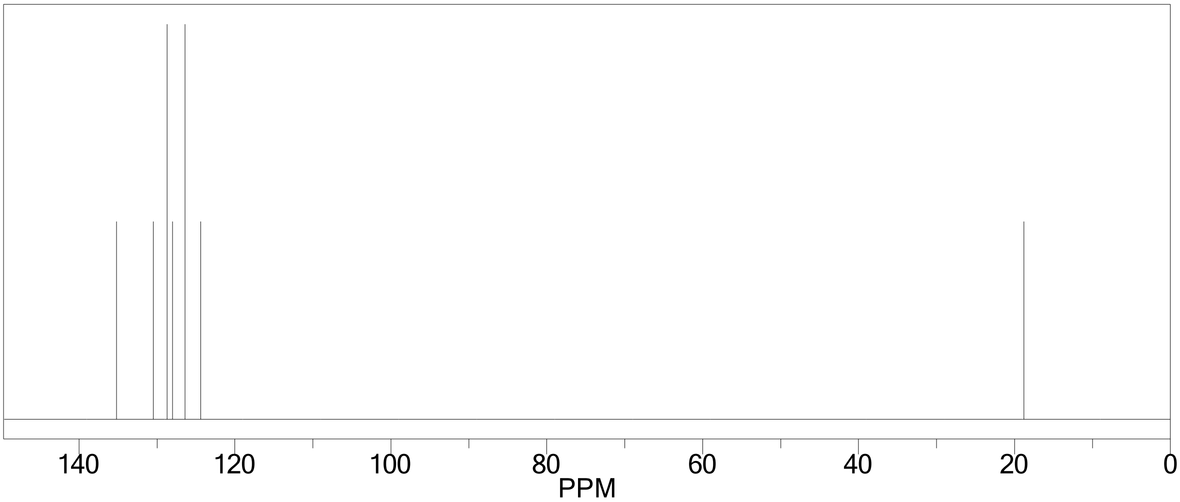


15. Peak clusters in the 7-9 ppm region are almost always indicative of H's attached to a benzene ring. (As we will learn later, the region from 7-9 ppm is called the aromatic region, and molecules containing a benzene ring are by far the most common type of aromatic molecule).

    Peak clusters in the aromatic region often overlap one another. For example, the mass of peaks between 7.3 and 7.4 ppm on the spectrum below is actually two overlapping peak clusters: a doublet of doublets worth 2H's overlapping with a triplet worth 1H.

    Draw one structure that goes with both spectra on this page.





16. (Check your work) How can you tell the top spectrum on this page is a proton NMR spectrum and the bottom spectrum is a carbon NMR spectrum?

17. (Check your work) According to the CMR spectrum, how many unique C's are there?

18. (Check your work) Explain why, on the proton NMR spectrum, the peak at 6.1 is expected to be a doublet of quartets.

19. The spectrum below goes with one of the diasteriomers shown. The other diasteriomer is the answer to the previous question.

Memorization Task L4.8: Splitting between *trans* H's is larger than between *cis* H's

It turns out that splitting between two H's that are *trans* to each other is larger than splitting between two H's that are *cis* to each other. This is often used to identify whether a molecule is *E* or *Z*.

Splitting is usually reported as a **J value** *in a unit called Hertz (Hz).*

[peak difference in ppm] = [peak difference in Hz]/[frequency of the spectrometer in megahertz (MHz)]

A typical NMR spectrometer operates at a set frequency somewhere between 200-600 megahertz (MHz), though some are as large as 1 GHz (1000 MHz). For example: If J = 10 Hz on a 200-MHz instrument, the splitting will be 0.05 ppm. This same 10 Hz splitting translates to a 0.02ppm splitting on a 500-MHz instrument, and a 0.01ppm splitting on a 1-GHz instrument. That is, the relative space between peak clusters increases, while the space between peaks within a given cluster, decreases.

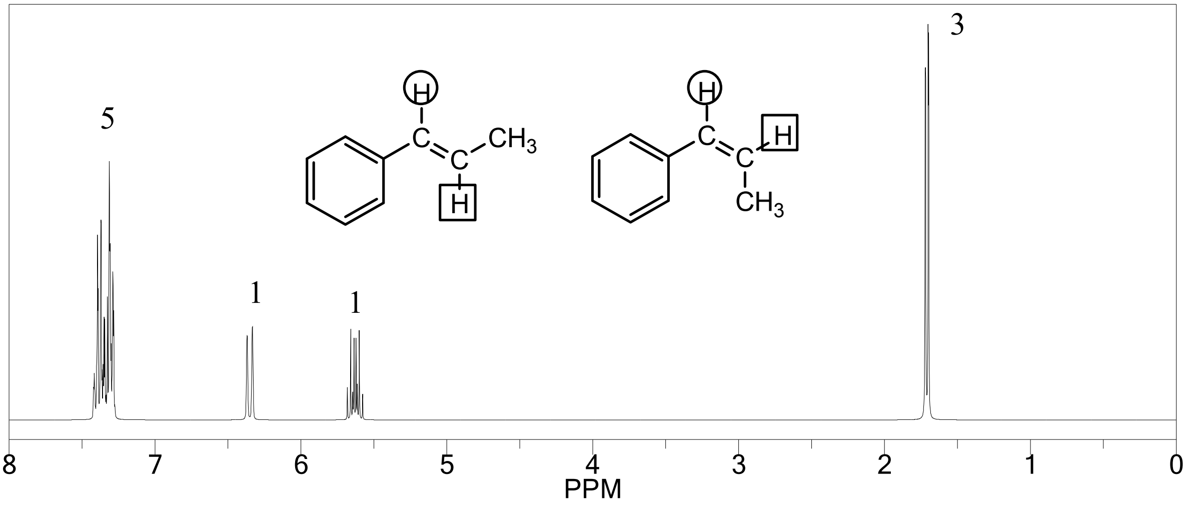
a. Splitting between the circled and boxed H's below can be measured by looking at either the peak cluster of the circled H or the boxed H; however, the cluster associated with the boxed H is much harder to interpret since it is a doublet of quartets! Identify the peak cluster that goes with the circled H, and confirm that ONLY the boxed H is near enough to split this peak.

b. On which proton NMR spectrum (the one below or the one on the previous page) is the splitting between the circled and boxed H's largest?

c. Cross out the structure below that does NOT go with the spectrum, and explain your reasoning.

d. Number or letter the H's on the remaining structure and use these to assign each unique type of H to a cluster on the spectrum. (Note that there are some overlapping clusters near 7.4 ppm.)

e. (Check your work) The structure that you crossed out below goes with the NMR spectra on the previous page. Draw this structure on the previous page, and assign each H to a peak cluster on the proton NMR spectrum and each C to a peak on the carbon NMR spectrum.



20. Read the assigned pages in the text and do the assigned problems.

The Big Picture

Proton NMR works in much the same way as carbon NMR, but again interpretation of the spectra is a much more important skill for an organic chemist than understanding the complex physics behind the instrument. The key elements of a proton NMR spectrum are reviewed below.

Common Points of Confusion

The following is a summary of the key elements of proton NMR:

- **ppm** or **chemical shift** (*given by location along the x axis*) tells you the amount of electron density around an H. The closer the H is to an electronegative element, the more "**deshielded**" it is and therefore the higher the ppm number of its peak cluster (farther left on the spectrum). Multiple bonds also cause the signal of nearby H's to be shifted to the left. Memorization Task L4.5 gives "chemical shifts" for common functional groups. Each chemically distinct H should have a unique chemical shift, though in practice different peak clusters sometimes overlap just by coincidence. This is a bigger problem in proton NMR than in carbon NMR (especially in the so-called "aromatic region" from 7-9 ppm), since most proton NMR peaks are squeezed into just an 8 ppm range (1-9 ppm).
- Peak area, not peak height, tells you the relative number of H's associated with a peak cluster.
- **Integration** or **peak cluster area** *(given by a number above or below a peak cluster, or by a line stepping up from left to right called the integration line)* tells you the relative area of each peak and therefore the relative number of equivalent H's represented by each peak. Note that integration gives you only a ratio of peak areas, making it impossible to tell the difference between a 1H to 3H ratio and a 2H to 6H ratio.
- Splitting in carbon NMR tells you the number of H's attached to a given carbon. For this reason, students incorrectly assume that splitting in proton NMR tells you the number of H's associated with a peak cluster. In fact, it is a bit more complicated (see next bullet).
- **Multiplicity** is the number of peaks in a peak cluster (also called **splitting** or **proton-proton coupling**). It tells you the number of nonequivalent neighbor H's within three bonds. For example, a doublet (two peaks) tells you there is exactly one non-equivalent H within three bonds of the H responsible for this signal.
- Equivalent H's do NOT split each other.

ChemActivity 17: Conjugation and MO Theory

(How can we make predictions about excited states of molecules?)

Model 1A: (*Review from CA 14*) *p* Orbital to *p* Orbital Conjugation

Neighboring *p* orbitals that are parallel to one another can interact to form a bond-like attraction. This attraction (called **conjugation**) is favorable and lowers the overall potential energy of the molecule.

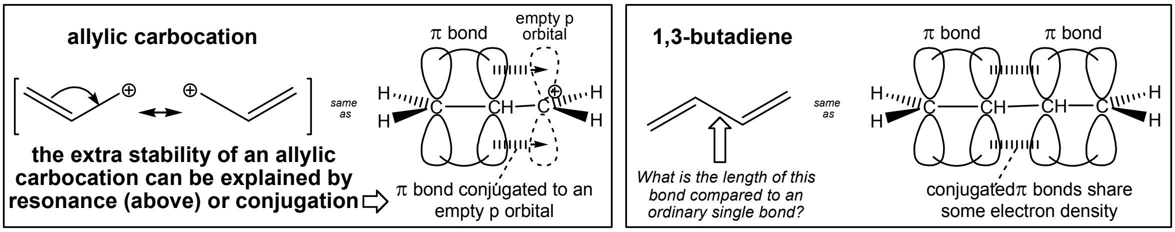
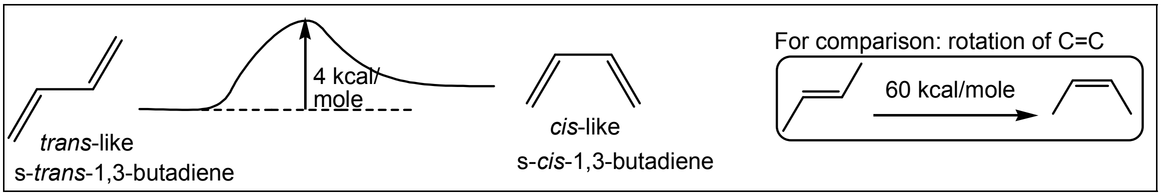

allylic carbocation
same as
π bond
empty p orbital
the extra stability of an allylic carbocation can be explained by resonance (above) or conjugation
π bond conjugated to an empty p orbital
1,3-butadiene
same as
π bond
π bond
What is the length of this bond compared to an ordinary single bond?
conjugated π bonds share some electron density

Figure 14.1: Examples of conjugation in an allylic carbocation and 1,3-butadiene

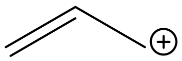
Conjugation of the two double bonds in 1,3-butadiene creates two conformations that are separated by a small activation barrier. In contrast to the 60 kcal/mole barrier separating a *cis* and *trans* double bonds, this 4 kcal/mole barrier is easily overcome at room temperature and is not considered a reaction.



Model 1B: History of Theories Describing Bonding

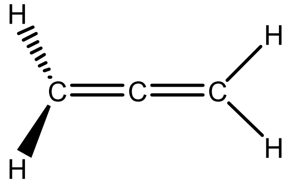
Lewis theory was developed in the late 1800s to explain observations that were possible then. Since that time, experiments have yielded deeper insight into the nature of molecules—properties and behavior that **Lewis theory cannot explain**. *For example:*

How do we explain the existence of the following apparent 1° carbocation?

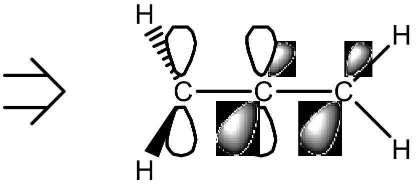


Answer: We invented resonance theory.

How do we explain the non-planar geometry of propan-1,2-diene (allene)?



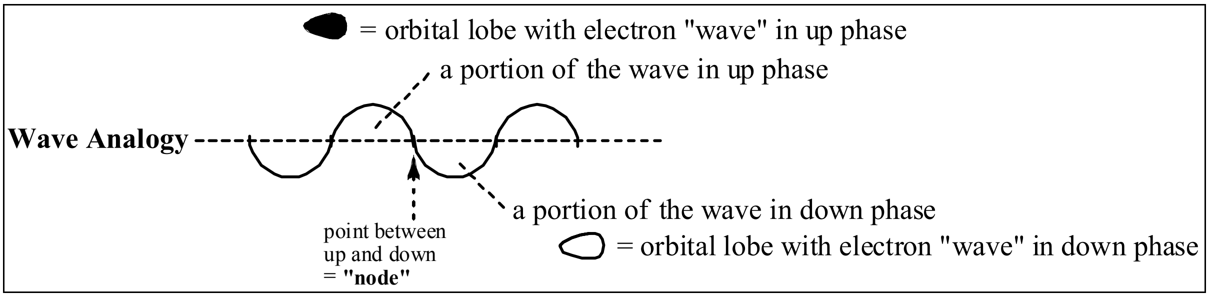
Answer: We invented hybridization theory.



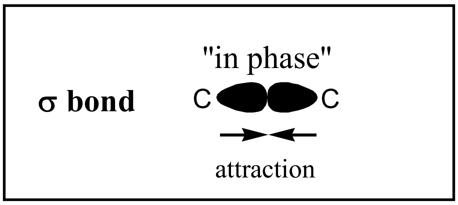
In this ChemActivity you will learn about yet another theory: **molecular orbital theory (MO theory)**. Just as hybridization and resonance did not replace Lewis theory, MO theory does not replace the other methods of prediction you have learned in this course. We will see that MO Theory has specific uses.

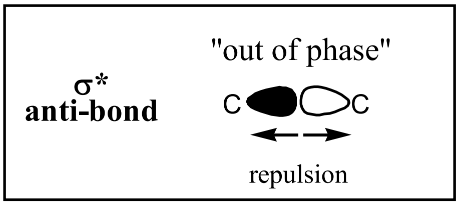
Model 1C: σ Bonding and σ* Anti-bonding

- MO theory makes a big deal of the wave nature of electrons.
- A wave has two possible phases: up and down.
- For **orbitals**, we can represent one phase as black and the other phase as white.


= orbital lobe with electron "wave" in up phase
a portion of the wave in up phase
Wave Analogy
a portion of the wave in down phase
point between up and down = "node"
= orbital lobe with electron "wave" in down phase

- If orbital lobes have **same phase = bonding** (attraction).
- If orbital lobes have **opposite phases** = **anti-bonding** (repulsion).





- Each of the orbital overlaps shown above are considered ***one*** **molecular orbital**.
- Molecular orbitals are arranged according to potential energy on a **MO diagram**.

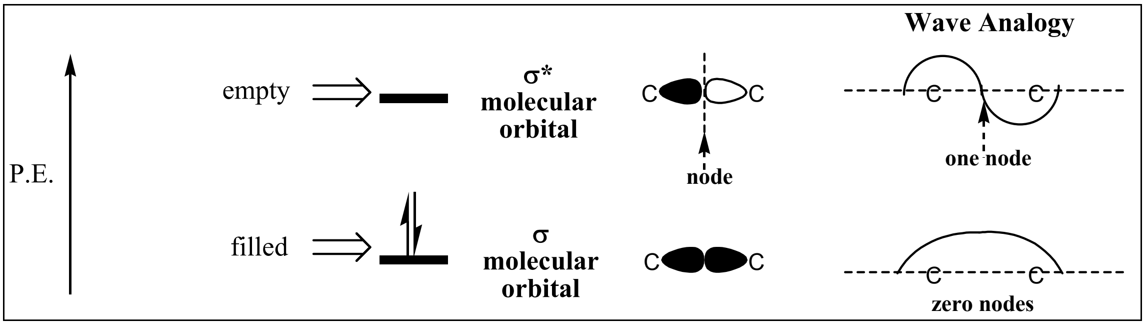
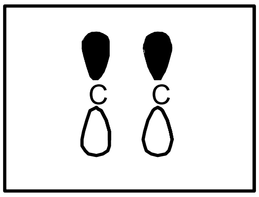


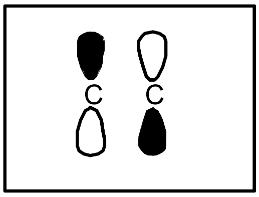
Figure 17.1: MO (molecular orbital) Diagram of a Carbon-Carbon σ bond

- Any molecular orbital can hold **zero (empty), one (half-filled) or two (full)** electrons.
- A "**node**" is a line of zero electron density that occurs between two out-of-phase orbitals.
- A full σ bond consists of a filled σ bonding MO and an empty σ* anti-bonding MO
- If the σ* anti-bonding MO were filled, it *would* exactly cancel out the attraction of the bonding MO. In Figure 17.1 the σ* anti-bonding MO is empty so it has no effect at all.

Critical Thinking Questions

1. (E) Label one of the overlaps below as "π **bond**" and the other as "π* **anti-bond**."





2. (E) What is the maximum number of electrons that can fit in a molecular orbital (MO)?
3. (E) Which is higher in potential energy, a **σ* anti-bonding MO** or a **σ bonding MO**?
4. According to MO theory, would it strengthen or weaken the C-C attraction if we added one electron to the MO diagram shown in Figure 17.1? Explain your reasoning.

Term Introduction: π system

The **π system** of a molecule consists of its π bonds, *p* orbitals, and all electrons in those bonds/orbitals.

5. How many electrons are there in the π system of ethene ($H_2C{=}CH_2$)?

6. Add electrons to the MO diagram of the π system of ethene, below, beginning with the lowest potential energy molecular orbital.

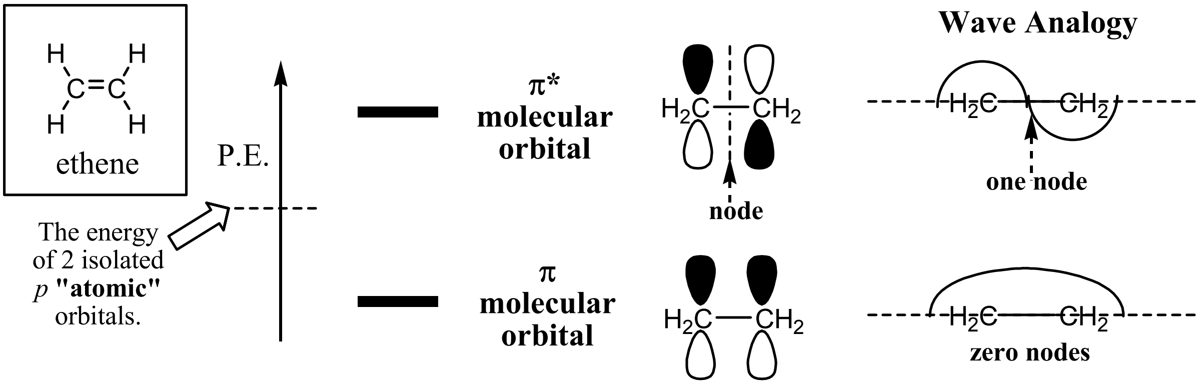
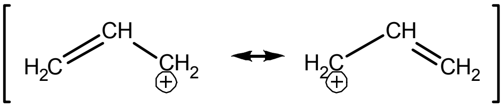


Figure 17.2: Incomplete MO Diagram of the π System of Ethene

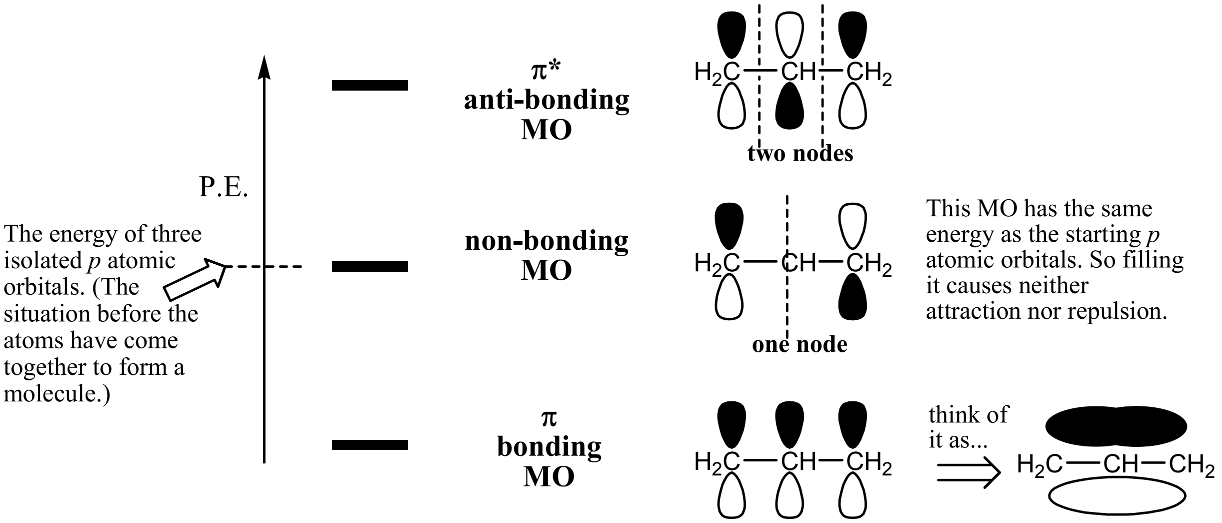
7. (Check your work.) Explain why the π* (anti-bonding) molecular orbital has no effect in this case.

8. The molecular orbitals (π and π*) in Figure 17.2 are generated by bringing two *p* **atomic orbitals** together in the two possible ways (in-phase overlap and out-of-phase overlap). According to Fig. 17.2, how do the PE's of the π and π* MO's compare to the PE of the original *p* atomic orbitals?

9. How many electrons are there in the π system of the allylic carbocation shown below using resonance?



10. Add electrons to the MO diagram below to generate a description of the π system of the **allylic carbocation** above.



The energy of three isolated *p* atomic orbitals. (The situation before the atoms have come together to form a molecule.)

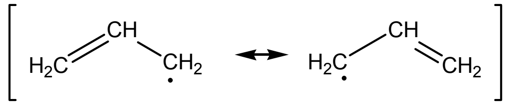
This MO has the same energy as the starting *p* atomic orbitals. So filling it causes neither attraction nor repulsion.

think of it as...

Figure 17.3: MO Diagram of an Allylic π System

11. How many electrons are there in the π system of the **allylic radical** below?

resonance description of **allylic radical**



12. Add an appropriate number of electrons to the MO diagram in Figure 17.3 so as to change it into an MO diagram of the allylic radical.

   a. According to your new MO diagram of an allylic radical, on which C or C's does the unpaired electron reside. (These carbons are said to have "radical character.") *Assume the unpaired electron is spread evenly through all lobes of the molecular orbital in which it resides.*

   b. (Check your work.) Do you get the same answer if you use the *resonance description* of an allylic radical to determine which carbon atoms have radical character?

   c. According to MO theory, do you expect the carbon-carbon bonds in an allylic radical to be…

      (1) Stronger than the C-C attractions in allylic carbocation

      (2) Weaker than the C-C bonds attractions in allylic carbocation

      (3) The same strength as the C-C bonds attractions in allylic carbocation.

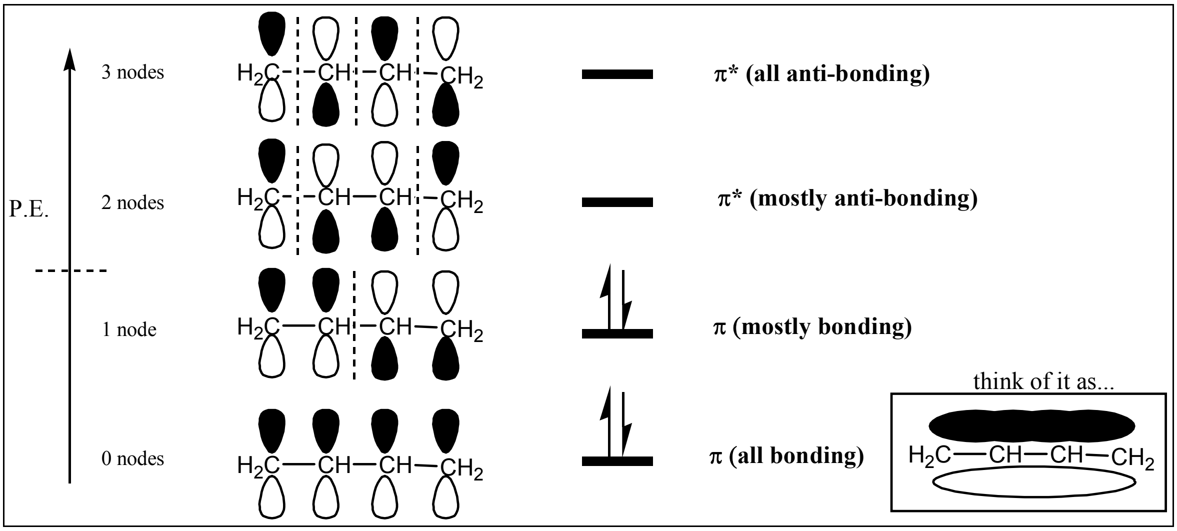
13. Draw a resonance description of the species that results if you add a **fourth** electron to the molecular orbital diagram in Figure 17.3.

   a. Based on your resonance description of an allylic anion above, which two carbons share the negative charge?

   b. Do you get the same answer if you use the MO diagram of an allylic anion (Figure 17.3 with four electrons) to determine which carbons share the negative formal charge? Explain.

Model 2: Molecular Orbital Description of 1,3-Butadiene

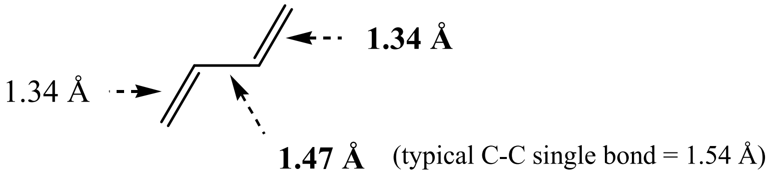
The π system MO diagram for **1,3-butadiene** is made by mixing the four *p* orbitals in all possible ways.



Critical Thinking Questions

14. According to previous models in this ChemActivity, what does the dotted line halfway up the potential-energy scale above represent?

15. Use the MO description of 1,3-butadiene to explain why the C_2-C_3 bond of butadiene is slightly shorter than a typical single bond. (Previously we explained this by citing conjugation.)

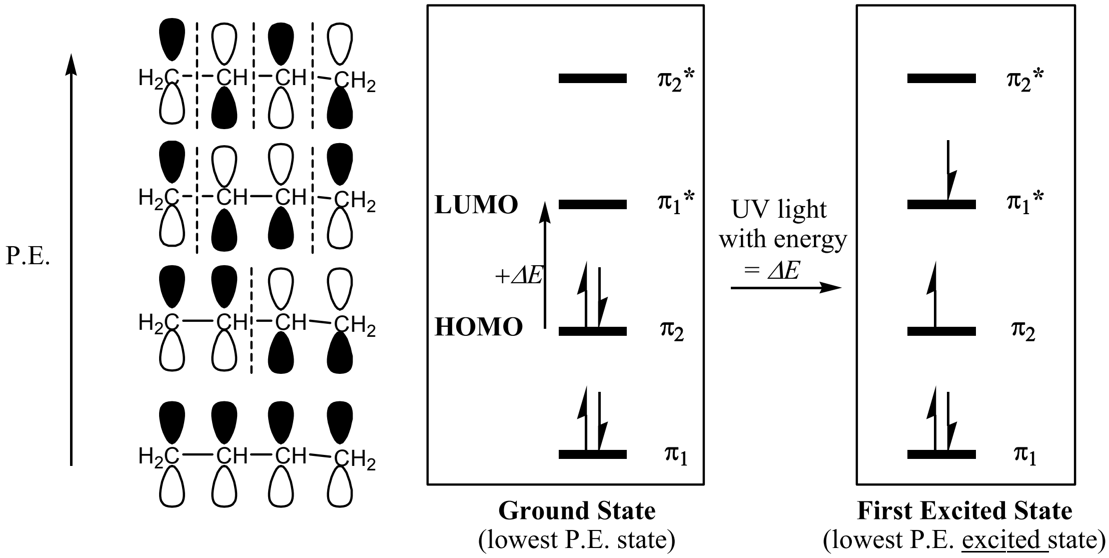


Model 3: Excited States of 1,3-Butatdiene

One of MO theory's great advantages over other theories is that it can be used to make predictions about a molecule that is not in its lowest P.E. state. These higher P.E. states are called **excited states**.

A molecule will absorb light if the energy/frequency of that light matches the energy difference (ΔE) between an **occupied molecular orbital** and an unfilled orbital. The easiest excitation is usually from the **HOMO (Highest Occupied Molecular Orbital)** to the **LUMO.**

For example, light of energy, ΔE, excites one electron from the **HOMO** to the **LUMO** of 1,3-butadiene, resulting in the lowest P.E. excited state (= **first excited state**) of 1,3-butadiene.



Ground State (lowest P.E. state)

First Excited State (lowest P.E. excited state)

Figure 17.4: Ground and 1st excited state of 1,3-butadiene

Critical Thinking Questions

16. Speculate what each letter in the acronym **LUMO** stands for.

Memorization Task 17.1: Energy is proportional to frequency ($E = h\nu$)

For example, the light that caused an excitation in Figure 17.4 would have a frequency (ν) = $\Delta E/h$, where h is a constant called Plank's constant.

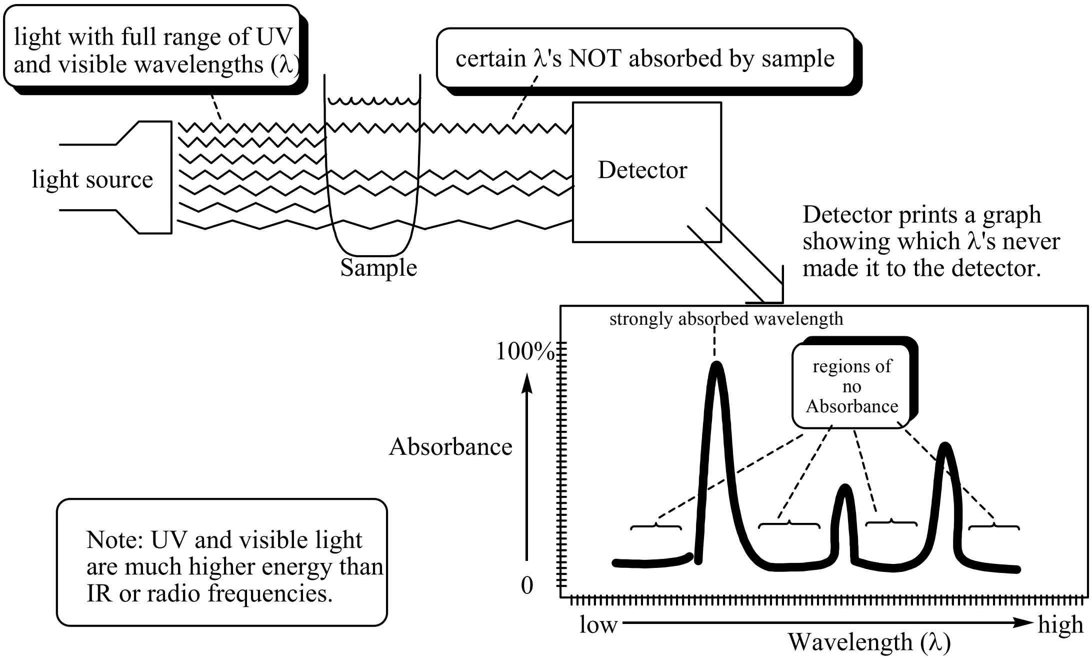
Note that wavelength (λ) is inversely related to energy/frequency: $\lambda = c \times 1/\nu$ (where c = speed of light)

17. When light with a frequency matching the HOMO-LUMO energy difference is shined on 1,3-butadiene, which bond(s) (e.g., C_1-C_2, or C_2-C_3) will be…
    a. strengthened?
    b. weakened?

18. Can you make a similar prediction using a hybridization or Lewis description of 1,3-butadiene?

Model 4: UV-Visible Spectroscopy

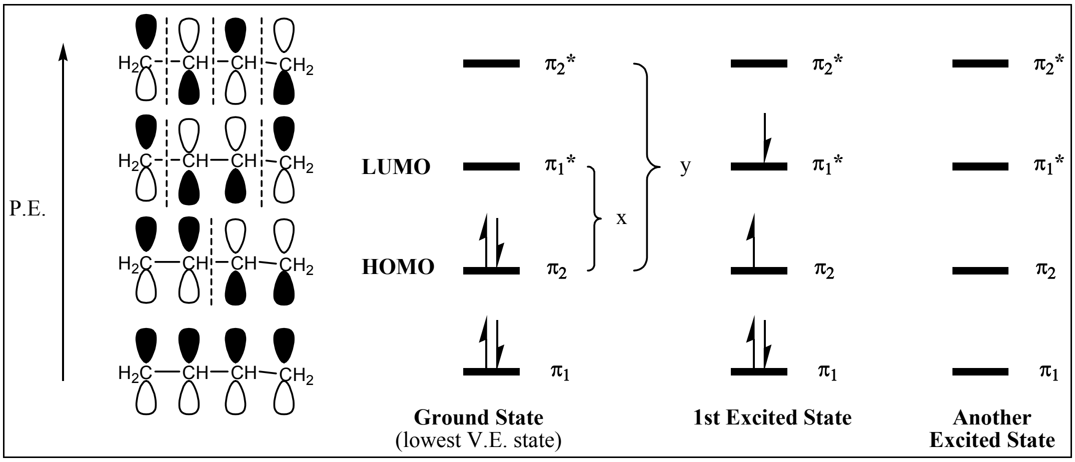
Light in the ultraviolet and visible range of the spectrum often has the correct energy to excite an electron from the HOMO to the LUMO or another unfilled molecular orbital.


light with full range of UV and visible wavelengths (λ)
certain λ's NOT absorbed by sample
light source
Sample
Detector
Detector prints a graph showing which λ's never made it to the detector.
strongly absorbed wavelength
regions of no Absorbance
100%
Absorbance
0
low
Wavelength (λ)
high

Note: UV and visible light are much higher energy than IR or radio frequencies.

Critical Thinking Questions

19. Consider the MO diagrams of the ground state and first excited state of 1,3-butadiene below. The distances **x** and **y** represent light of two different energies/frequencies/wavelengths.
    a. Absorption of which frequency of light (x or y) will result in the first excited state?
    b. Fill in the incomplete MO diagram. below right, to show the excited state that occurs when the sample absorbs light of frequency y.



20. What can you tell about a molecule from looking at its UV-visible spectrum?

21. Is your answer to the previous question consistent with the fact that, in organic chemistry, IR, MS, and NMR spectroscopies are usually more useful for determining structure than UV-vis spectroscopy?

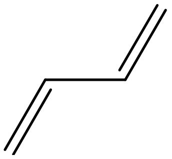
Exercises

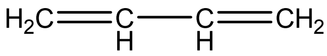
Observations:

- 1,3-butadiene exists in two distinct forms (*trans*-like and *cis*-like).
- 3.9 kcal/mole of energy are required to convert one to the other. (For comparison, it takes 60 kcal/mole to rotate a typical C=C double bond.)
- The C_2—C_3 bond of butadiene is shorter than an ordinary C—C single bond.

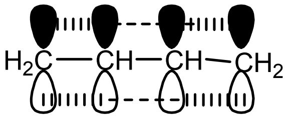
1. Explain the observations above using hybridization theory.
2. Explain the observations above using MO theory.

3. Consider the following representations of butadiene:





$H_2C{=}\underset{H}{C}{-}\underset{H}{C}{=}CH_2$



a. Each thin dotted line (----) on the farthest right representation of 1,3-butadiene above represents approximately…(choose the best answer below).

(1) a little less than one double bond (approximately 143 kcal/mole)

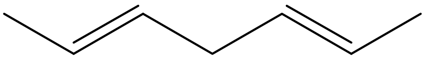
(2) a little less than one π bond (approximately 64 kcal/mole)

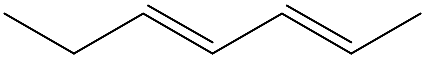
(3) a little less than half of one π bond (approximately 32 kcal/mole)

(4) 3 percent of one π bond (approximately 2 kcal/mole)

b. Each thick dotted line (|||||||||) on the farthest right representation of 1,3-butadiene above represents approximately…(choose the best answer from the same choices).

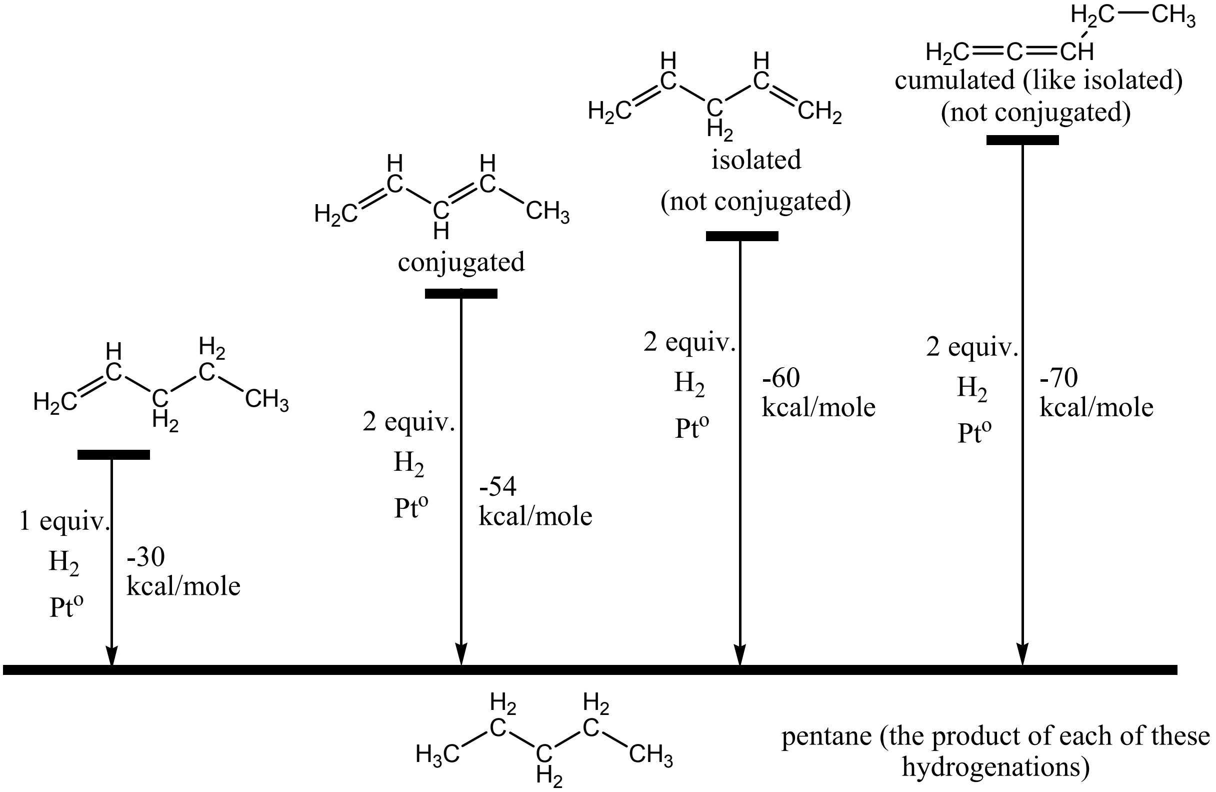
4. Consider the following dienes:





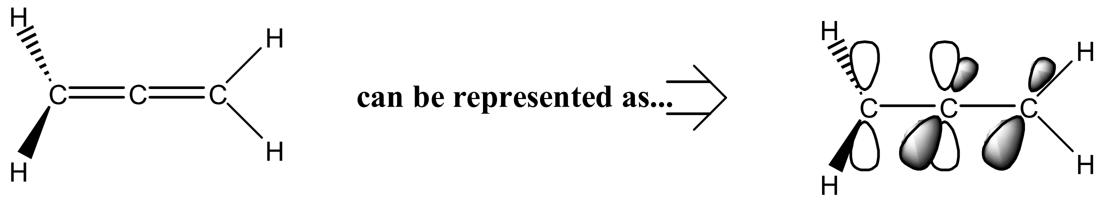
a. Explain why the diene on the right has more bonding interactions than the one on the left.

b. Predict which one will be lower in potential energy, and explain your reasoning.



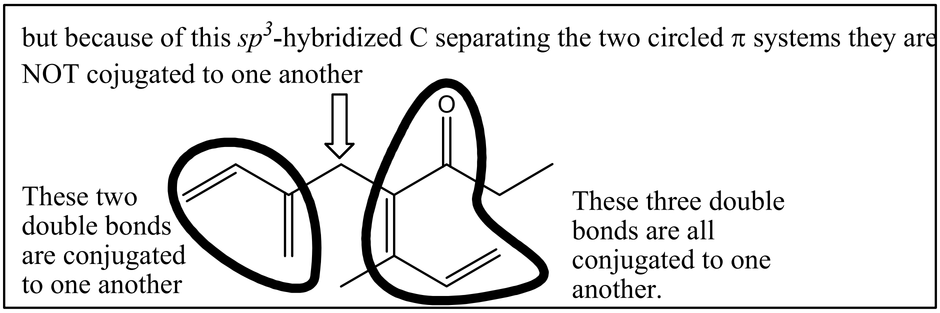
5. Consider the hydrogenation reactions above.
   a. T or F: When one molecule of H_2 is added to a double bond (in the presence of Pt metal) one π bond is broken, and two new C-H bonds are formed.
   b. T or F: A hydrogenation reaction is downhill in terms of potential energy. That is, more energy is released from bonds forming than is consumed to break bonds.
   c. T or F: The P.E. of two isolated π bonds = 2 x P.E. of one π bond.
   d. According to the reactions above, which is higher in potential energy, 1,3-pentadiene or 1,4-pentadiene?
   e. Construct an explanation for why 1,3-pentadiene is lower in P.E. than 1,4-pentadiene.

6. The following are representations of a molecule with a pair of **cumulated** double bonds. Construct an explanation for why the two π bonds in this molecule are isolated from one another, not conjugated.



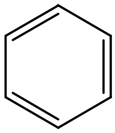
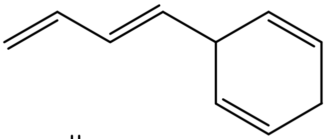
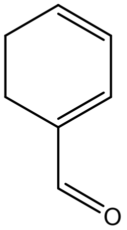
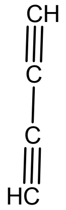
7. Explain why 1,3-butadiene is planar in its lowest potential energy conformation. (*Hint*: See the Review section on the first page of this ChemActivity.)

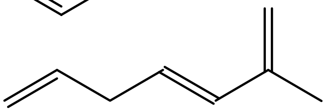
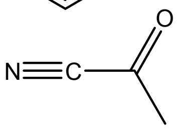
8. Double bonds that are not separated by an sp^3 carbon are said to be "**conjugated**." There is no limit to the number of double bonds that can be conjugated together. For each molecule below, circle together any double bonds that are conjugated to one another. The first one is done for you. (*Hint*: it may help to identify the sp^3 carbons.)


but because of this sp^3-hybridized C separating the two circled π systems they are NOT cojugated to one another

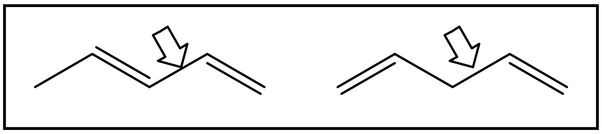
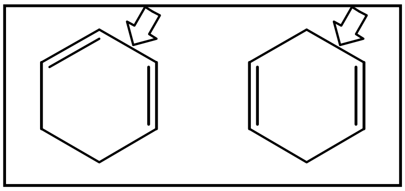
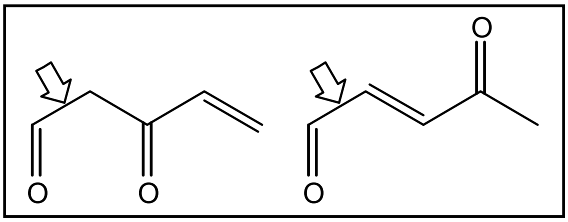
These two double bonds are conjugated to one another

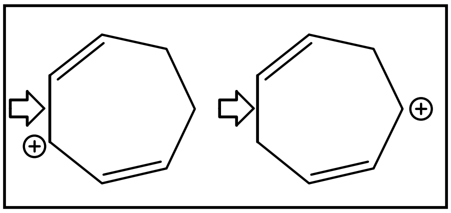
These three double bonds are all conjugated to one another.

9. For each box,
   a. predict which of the two species will be lower in potential energy.
   b. predict which of the two bonds indicated with an arrow will have a shorter bond length.

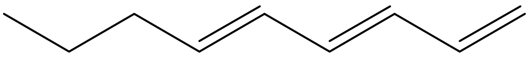


10. Draw an orbital representation of 1,3,5-hexatriene. Indicate each pi bond as a pair of bold dotted lines and each partial pi bond as a light dotted line as in Exercise 3.

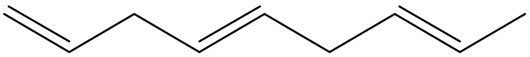
11. Exactly two of the pi bonds in 1,2,3-butatriene (shown below) are conjugated to one another. Indicate which two, and explain why the third pi bond is not conjugated to the other two.

$$H_2C{=}C{=}C{=}CH_2$$

12. Use the heats of hydrogenation in Exercise 5 to calculate the most likely heat released (in kcal/mole) during catalytic hydrogenation of each triene below. Assume complete hydrogenation so that the product is nonane in each case. Choose the best answer from A-D for each structure.

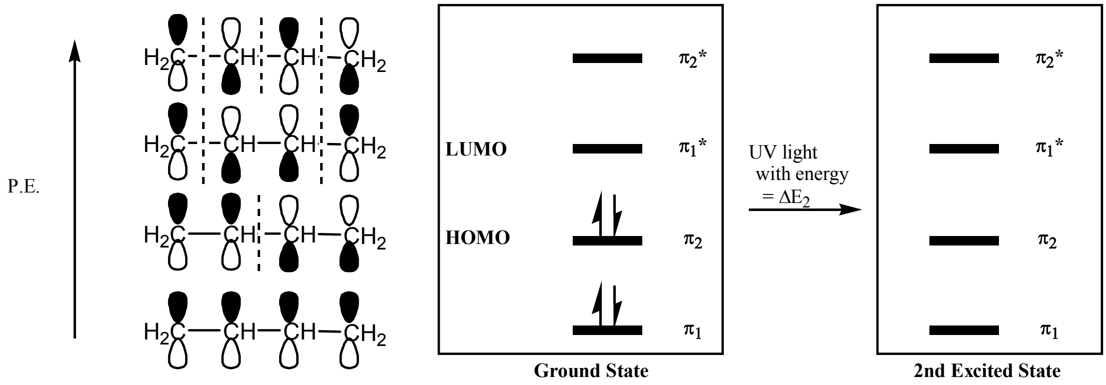


A. 93 kcal/mole
B. 90 kcal/mole
C. 87 kcal/mole
D. less than 84 kcal/mole

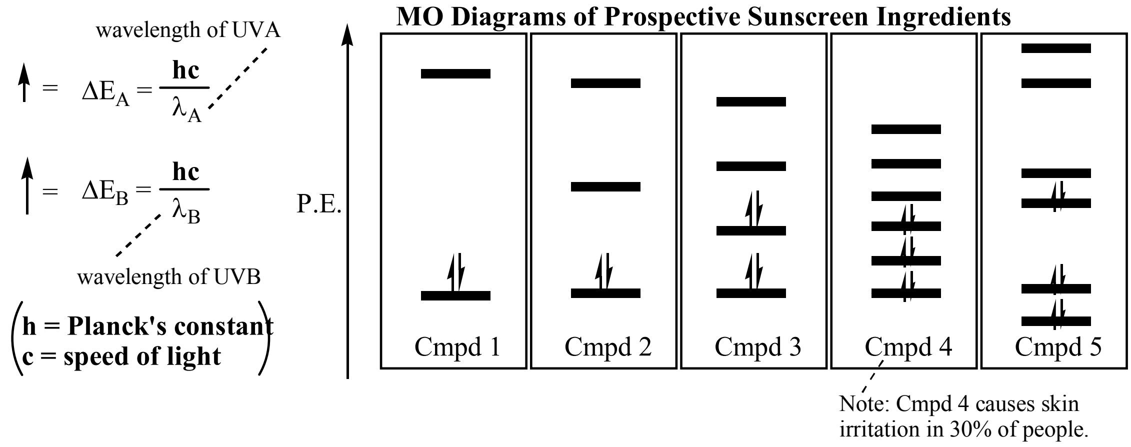


A. 93 kcal/mole
B. 90 kcal/mole
C. 87 kcal/mole
D. less than 84 kcal/mole

13. Draw an arrow on the ground state MO diagram below showing the magnitude of ΔE_2, the energy required to excite an electron in the HOMO of 1,3-butadiene to the highest anti-bonding orbital. Then complete the MO diagram of this second excited state.



14. Sunburn is caused, principally, by two wavelengths of UV light called UVA and UVB. The energy of each of these is represented by an arrow, below.


wavelength of UVA
= $\Delta E_A = \frac{hc}{\lambda_A}$
= $\Delta E_B = \frac{hc}{\lambda_B}$
wavelength of UVB
h = Planck's constant
c = speed of light
P.E.
MO Diagrams of Prospective Sunscreen Ingredients
Cmpd 1
Cmpd 2
Cmpd 3
Cmpd 4
Cmpd 5
Note: Cmpd 4 causes skin irritation in 30% of people.

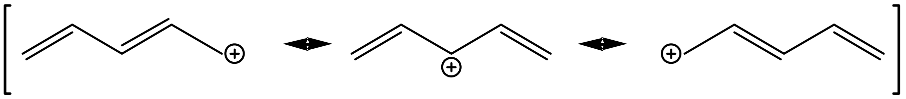
a. Which compounds above absorb light of the shortest wavelength (λ)?

b. If you were developing a sunscreen, which compound or compound(s) would you put in your product? Explain your reasoning.

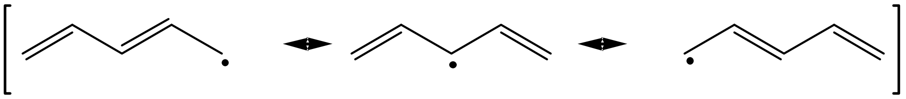
15. Use the following rules to fill in the electrons in the MO diagram below to represent the cation, radical, and anion shown.

- The number of *p* atomic orbitals in π system = the number of molecular orbitals in MO diagram. (*For example: For 1,3-butadiene, you start with four p orbitals and end up with four MO's.)*
- MO's have zero, one, two, three…etc. nodes (going from lowest to highest P.E.)
- Placement of nodes must be symmetrical. (*e.g., if one node, it must be in the middle.*)
- Fill MO's with electrons starting from the lowest P.E. MO.

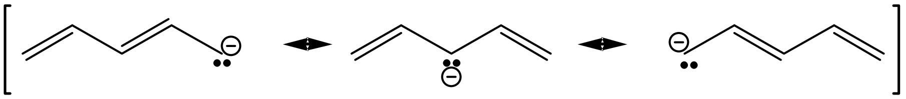
with 4 pi electrons it describes the following carbocation:

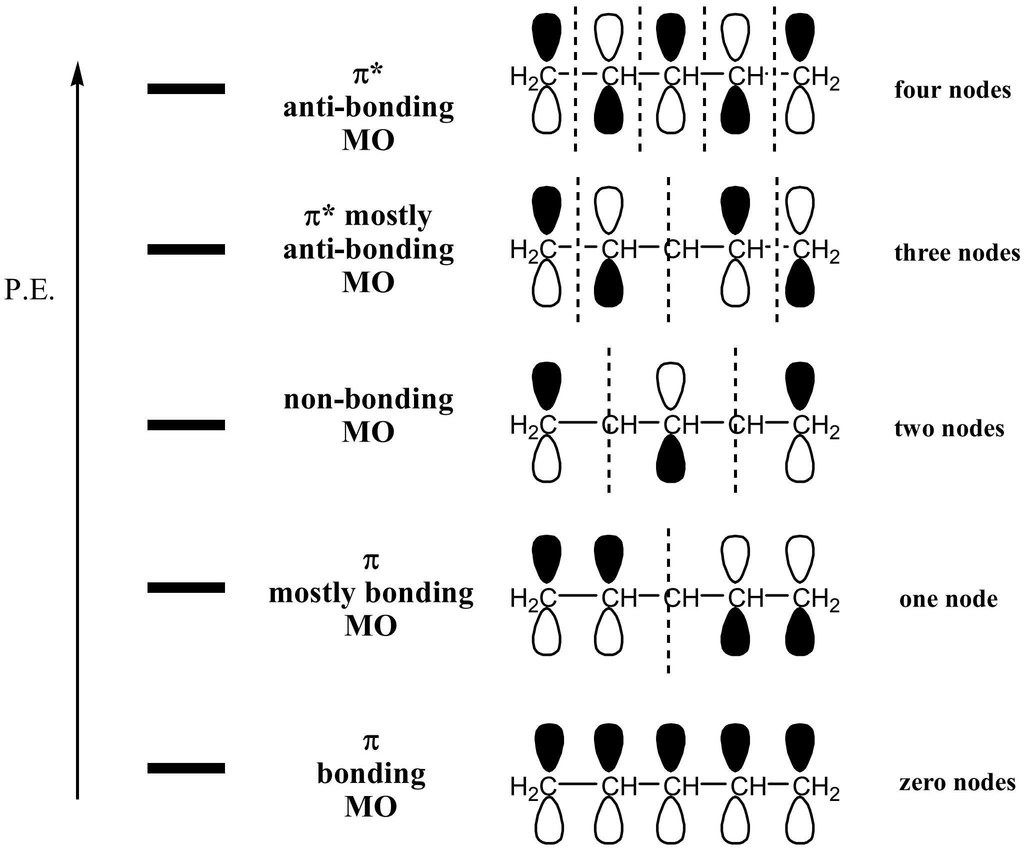


with 5 pi electrons it describes the following radical:



with 6 pi electrons it describes the following carbanion:





16. Use the rules for drawing MO diagrams to construct an MO diagram for 1,3,5-hexatriene.

17. Read the assigned pages in your text, and do the assigned problems.

The Big Picture

Molecular orbital theory is a tool that is used more frequently in advanced organic courses than in this course. This activity is designed as a brief introduction to the topic. Though you may be asked to generate a simple MO diagram of the pi system of a small symmetrical molecule, generating an MO diagram of a complex or asymmetrical molecule is a task beyond the scope of this course. Most predictions we will make in this course will use the older, simpler tools we have become familiar with like Lewis structures, resonance structures, and hybridization.

The key exception appears in the next activity, in which we use MO theory to explain why benzene and other so called "aromatic" molecules are unusually stable and low in energy.

UV-visible spectroscopy is mostly used to determine energy gaps on an MO diagram (e.g., the difference between the HOMO and the LUMO. This can tell you about the symmetry of a molecule, but does not give direct structural information like IR, NMR, and MS.

Common Points of Confusion

p orbitals can be conjugated only when they are parallel and neighbor one another.

MO theory relies on the wave nature of electrons, which is very strange and abstract. Accept on faith the strange premises of **MO theory**, for example…

- An electron can be delocalized over all lobes of a molecular orbital. (You may want to think of it as a fine mist of negative charge rather than a discrete particle.)
- An electron can be found in either lobe of a *p* orbital, but can NEVER be found on the node separating these lobes. (In fact, the electron is said to move from one lobe to the other via something called quantum mechanical "tunneling.")
- A molecular orbital can exist without any electrons in it. Think of it as a sort of ghost orbital that has no effect until it is populated with one or two electrons.
- Multiple molecular orbitals can exist in the same region of space, even when both are populated with electrons. For example, the two π bonding orbitals in Figure 17.4 occupy approximately the same space.
- In the next activity we will see symmetrical MO diagrams in which two different MO's have exactly the same potential energy. These are called "**degenerate MO's**"—this name comes from the mathematics and is not a moral condemnation of these molecular orbitals.

ChemActivity 18: Aromaticity

PART A: AROMATICITY

(What structures are likely to exhibit the special stability known as **aromaticity**?)

Model 1: Amazing Benzene!

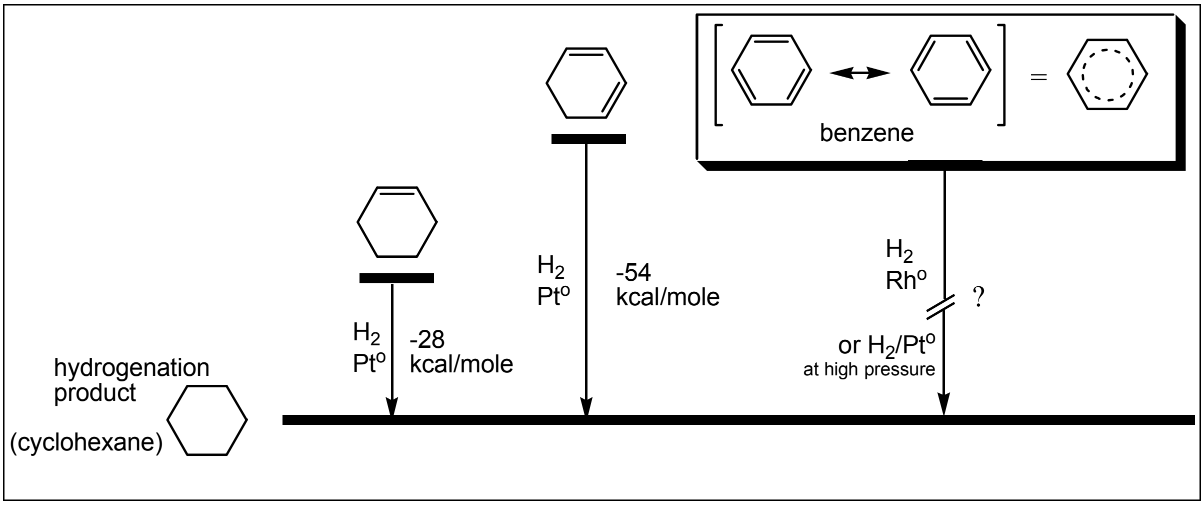
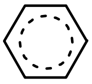


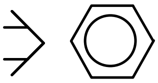
Figure 18.1: Heats of Hydrogenation

Critical Thinking Questions

1. (E) What property of benzene does the dotted-line circle emphasize?



It turns out that it is much faster to draw a solid-line circle so you will often see benzene drawn this way



2. Based on the data in Figure 18.1, estimate the heat of hydrogenation for benzene. (Note that it takes an exotic rhodium catalyst or extreme conditions to reduce benzene to cyclohexane.)

3. The heat of hydrogenation of benzene is actually –49kcal/mole.
   a. Add a solid line to Figure 1 indicating this value for benzene.
   b. Is benzene more or less stable than predicted based on the heats of hydrogenation of cyclohexene and 1,3-cyclohexadiene?

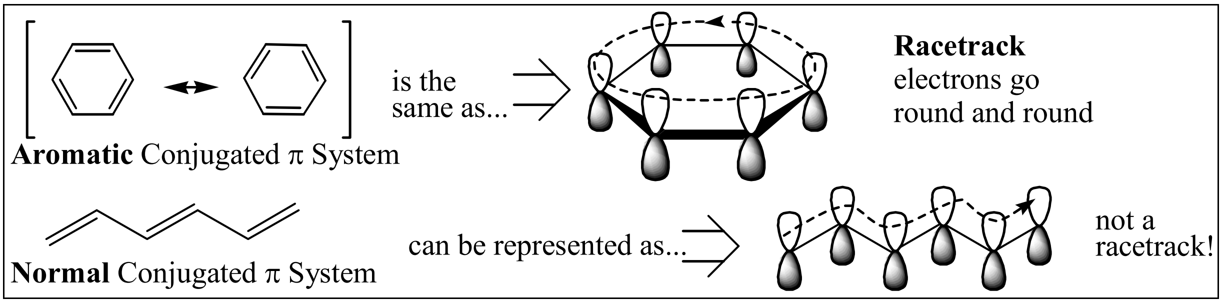
Term Introducton: Aromatic Molecules and Aromaticity

- Benzene and other similar molecules exhibit an almost magical stability (lower than expected potential energy). These molecules are called **aromatic molecules**.
- Before it was understood, this “magical stability” was named **aromaticity** because many molecules in this class have a strong **aroma** (smell).
- Resonance alone cannot explain this amazing stability.

Model 2: Cyclic Conjugated π Systems (“Racetrack” Analogy)

Recall from ChemActivity 5 that an electron in a larger “box” has a longer wavelength and so is lower in potential energy than an electron confined to a smaller “box.”

The “racetrack” analogy states that the electrons of benzene are low in P.E. because they reside in a “box” that is effectively very large due to the fact they can race endlessly around a track of conjugated *p* orbitals. We call this “racetrack” of *p* orbitals a **cyclic conjugated pi system**.



is the same as...
Racetrack electrons go round and round
Aromatic Conjugated π System
can be represented as...
not a racetrack!
Normal Conjugated π System

Not all cyclic conjugated π systems are aromatic. Only those structures below that are labeled “**Aromatic**” display the special stability associated with aromaticity.

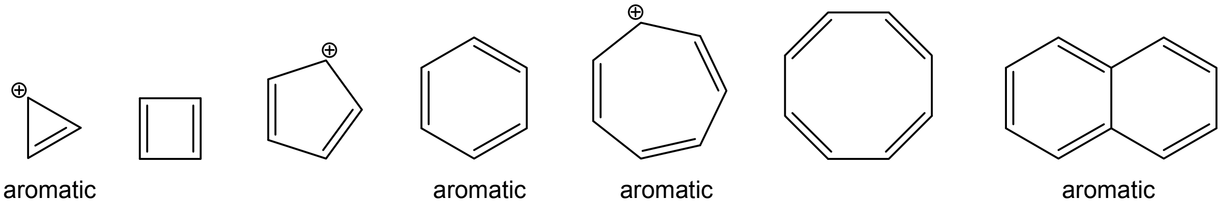


Figure 18.2: Examples of cyclic conjugated π systems

Critical Thinking Questions

4. Confirm that there is a *p* orbital (empty or half-filled) at each carbon in Figure 18.2.

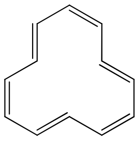
    a. Find the largest possible cyclic conjugated π system in each molecule in Figure 18.2, and label it with the total **number of electrons in that π system** (the electrons in the *p* orbitals of the largest racetrack).

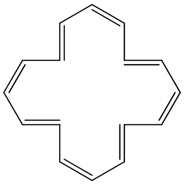
    b. Certain “magic numbers” of π electrons give rise to aromaticity. According to the data in Figure 18.2, circle the “magic numbers” in the list below.

    2 4 6 8 10 12 14 16 18 20

    c. Continue the series past 10 electrons: Which of 12, 14, 16, 18, and 20 appear to fit the pattern and are expected to be "magic" numbers that allow aromaticity. Circle these above.

    d. Which of the following molecules is expected to be aromatic? Explain your reasoning.





Memorization Task 18.1: Hückel's Rule

In 1938 German chemist Erich Hückel noticed that molecules with 2, 6, 10, 14, 18, 22, etc., electrons in their cyclic conjugated π system displayed the special properties of aromatic molecules.

This came to be called "**Hückel's Rule**," which states: "**a cyclic, continuous, conjugated π system exhibits aromaticity (special stability) if it contains 4n + 2 π electrons** (where n = 0, 1, 2, 3…etc.)."

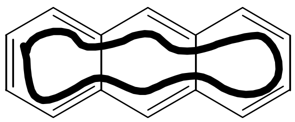
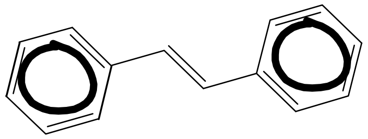
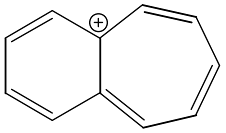
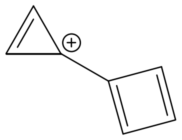
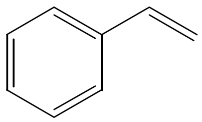
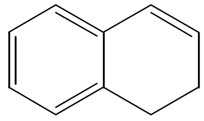
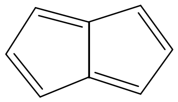
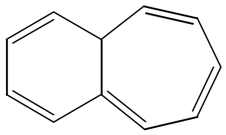
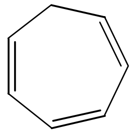
Critical Thinking Questions

5. (Check your work.) Are your answers on the previous page consistent with Memorization Task 18.1?

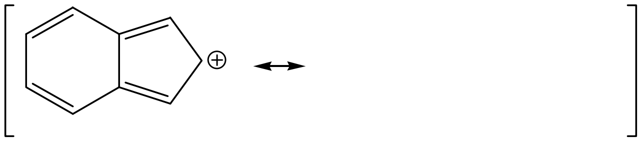
6. For a molecule to be considered aromatic it must simply contain an aromatic π system. (That is, there can be parts of an aromatic molecule that are not involved in the "racetrack.")

   a. **Cross out** the three molecules below that are **not aromatic** (**non-aromatic**).

   b. Trace each aromatic π system ("racetrack") in the remaining (aromatic) molecules. The first two are done for you. Note that the second example has two **aromatic rings**. Even though these two aromatic rings are conjugated together, they are NOT considered a single aromatic system (The molecule has two separate aromatic "racetracks.").

7. A molecule is aromatic if it has at least one resonance structure with a continuous cyclic π system containing 4n+2 π electrons. The cation below is aromatic, but the resonance structure shown does not demonstrate this! **(It does NOT contain an aromatic π system)**. Draw a different resonance structure of this molecule that contains an aromatic π system and shows this cation is aromatic.

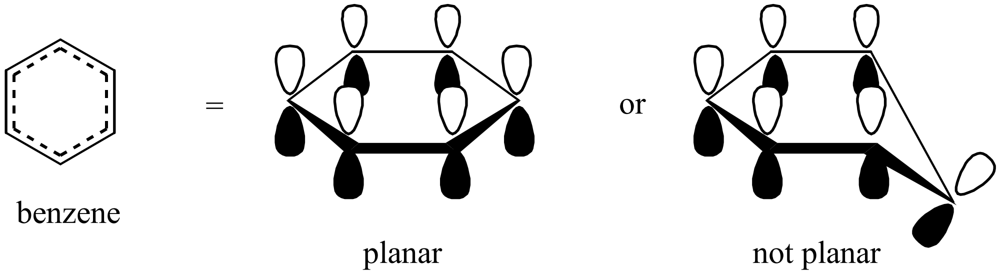


Note: There are a total of 11 resonance structures in this set. Only four of them contain an aromatic pi system. Draw them at home for practice.

   a. How many π electrons are involved in the aromatic resonance structure you drew?

   b. Which of the two resonance structures shown is more important? Explain your reasoning.

8. Consider the orbital representations of benzene below.

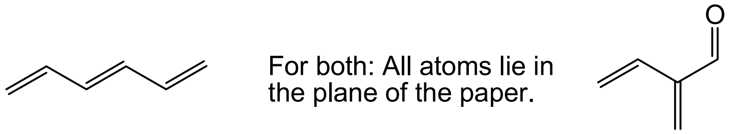


a. Which π system (planar or not planar) has the better *p* orbital racetrack?

b. Is your conclusion consistent with the fact that benzene is always planar?

c. Construct an explanation for why all conjugated π systems (not just aromatic ones) are lower in potential energy when they are planar.

For Example:

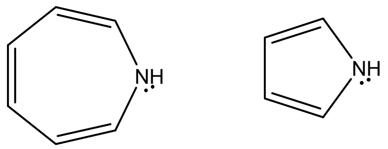


Memorization Task 18.2: Rule for determining when a lone pair will reside in a *p* orbital

A lone pair on an atom in a cyclic conjugated π system will occupy a *p* orbital (and become a part of the π system of the molecule) **if doing so makes the molecule aromatic**.

9. Construct an explanation for why an sp^3 hybridized atom in a ring interrupts any “p orbital racetrack” in that ring. (See last two examples in CTQ 6.)

10. Calculate the number of electrons in the π system of each molecule at right if…

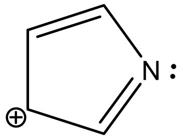


a. the lone pair on N resides in a *p* orbital.

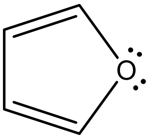
b. the lone pair on N resides in an sp^3 hybrid orbital (does not participate in the π system).

c. Predict which lone pair at right will reside in a *p* orbital and which will reside in an sp^3 hybrid orbital, and explain your reasoning.

11. Construct an explanation for why the lone pair on N in the molecule below CANNOT participate in the π system of the molecule (even though doing so would give the molecule 4n+2 π electrons). *Hint*: There is already a *p* orbital on the nitrogen. What is this *p* orbital doing?)



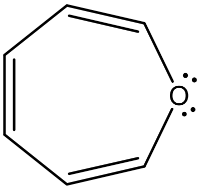
12. In the following molecule only one of the lone pairs on oxygen resides in a *p* orbital.



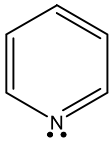
a. Explain why one lone pair on oxygen resides in a *p* orbital.

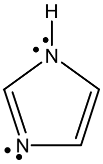
b. What is the hybridization state of the oxygen, and what type of orbital does the other lone pair on oxygen occupy?

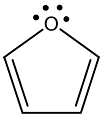
13. Can the following molecule be aromatic? Explain your reasoning.

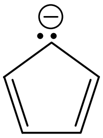


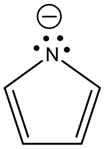
14. Indicate the type of orbital holding each lone pair, and label each molecule that is aromatic.











15. Review: For a molecule to be aromatic it must have a π system that …(***fill in the blanks***).

(1) is cyclic

(2) has a continuous set of ____________________ *p* orbitals (no sp^3 carbons in the ring)

(3) has __________ π electrons (2 or 6 or 10 or 14, etc.)

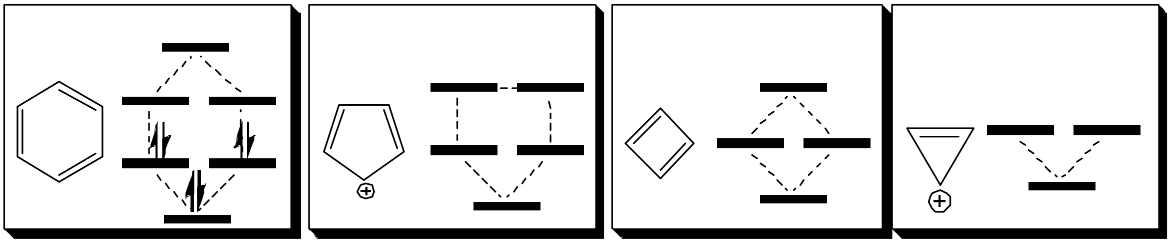
(4) and has an overall ________________ geometry allowing the *p* orbitals to be parallel.

PART B: MO EXPLANATION FOR AROMATICITY

(How can we explain aromaticity and anti-aromaticity using molecular orbital theory?)

Model 3: Molecular Orbital Diagrams of Cyclic π Systems

The **MO diagram** of a cyclic conjugated π system takes the shape of the ring involved, with one vertex pointing down. For example…



MO Diagram of Benzene (completed)

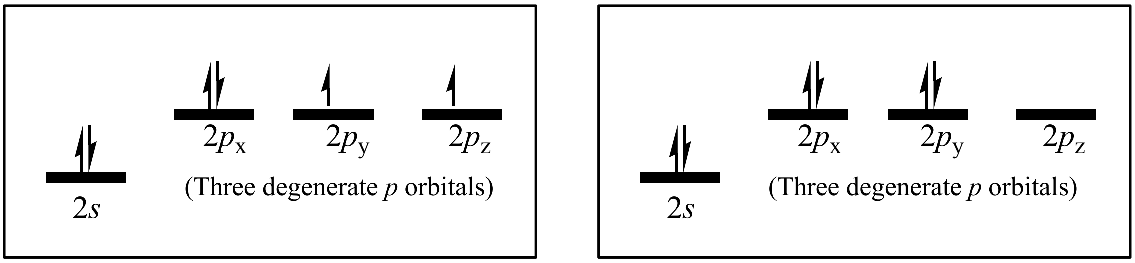
MO Diagrams of Other Cyclic Conjugated Pi Systems (electrons not filled in yet)

Figure 18.3: MO diagrams of cyclic conjugated π systems

Molecular orbitals on a MO diagram with the same energy are called **degenerate orbitals**.

All degenerate orbitals must be half-filled before any one is filled. For example…

Valence Electron Orbital Occupation for a Oxygen Atom


$2p_x$
$2p_y$
$2p_z$
(Three degenerate *p* orbitals)
2*s*
$2p_x$
$2p_y$
$2p_z$
(Three degenerate *p* orbitals)
2*s*

CORRECT

not correct

Critical Thinking Questions

16. Circle a pair of **degenerate** molecular orbitals on the MO diagram of benzene.
17. Add the appropriate number of electrons to the three other MO diagrams in Figure 13.3.

Memorization Task 18.3: Radical Character

A species with an unpaired electron is said to have "**radical character.**" Usually a species with radical character is very reactive.

18. Label two compounds in Figure 13.3 with the words "**has radical character-very reactive**."

19. Employing Hückel's Rule, label all **aromatic** species in Figure 13.3.

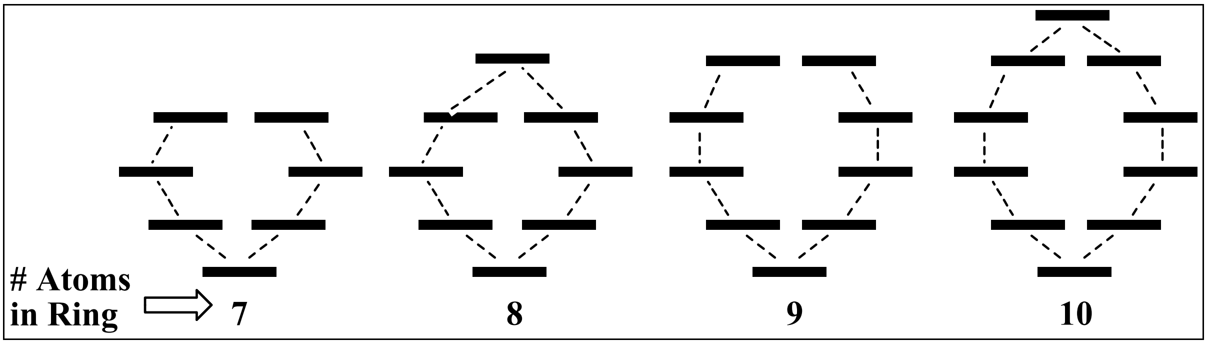


Figure 13.4: MO diagrams of 7-, 8-, 9-, and 10-atom cyclic conjugated π systems

20. Use the MO diagram of an 8-atom ring (above) to fill in the following table.

No. Of Electrons in the π System	2	4	6	8	10	12
Has Radical Character According to MO						
Aromatic (according to Hückel's Rule)						

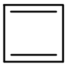
21. Confirm that you get the same answer to the previous question no matter which cyclic MO diagram you use to fill in the table (as long as there is room for all the electrons).

Term Introduction: Anti-Aromatic Molecules

A molecule is **anti-aromatic** (and highly reactive) if it exhibits all characteristics of aromaticity EXCEPT that it has 4n (instead of 4n+2) π electrons (e.g., 4, 8, 12, etc.).

22. Label each species in Figure 18.3 that is anti-aromatic.

23. Cyclobutadiene can be isolated and studied at temperatures lower than –200°C. At temperatures above –200°C it immediately reacts with itself to form other more stable products. Use molecular orbital theory to explain why **cyclobutadiene** is unstable.

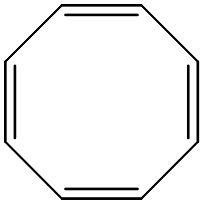


Cyclobutadiene (very unstable)

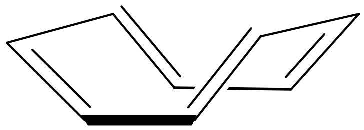
24. List four things about cyclobutadiene that make it anti-aromatic.

25. (Check your work.) Compare your answer to the previous CTQ to the last CTQ in Part A.

26. Cyclooctatetraene is quite stable at room temperature. However, close examination of the structure reveals that **it is not planar**. This can be explained by optimization of bond angles.



Cyclooctatetraene



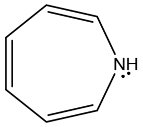
Cyclooctatetraene in its Preferred Conformation

   a. Use MO theory to construct an argument **not based on bond angle optimization** that explains why cyclooctatetraene is not planar.

   b. Cyclooctatetraene is considered **non-aromatic.** This means it is neither aromatic nor anti-aromatic. Explain.

27. Cyclobutadiene is one of the few molecules that is unable to "avoid" being anti-aromatic. Explain.

28. Construct an explanation for why the N on the following molecule is expected to be *sp*^{3} hybridized.



Memorization Task 18.5: Most molecules are non-aromatic & very few are anti-aromatic.

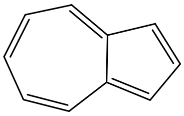
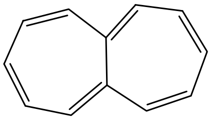
Cyclobutadiene is too small to adopt a nonplanar geometry. Most other cyclic conjugated π systems with 4n π electrons can flex to adopt a conformation that is not planar, or adopt a hybridization state that breaks the conjugated π system.

Bottom line: There are very few anti-aromatic molecules and many aromatic molecules, but the majority of molecules are neither aromatic nor anti-aromatic (these are called **non-aromatic**).

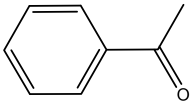
29. Draw an example of each of the following that does not already appear in this activity: an anti-aromatic molecule, an aromatic molecule, and a non-aromatic molecule.

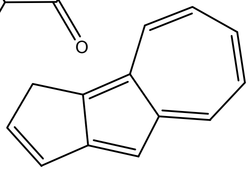
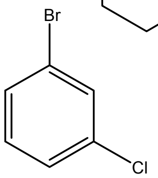
Exercises for Part A

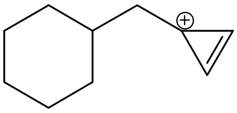
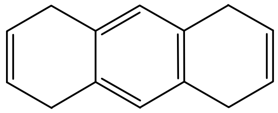
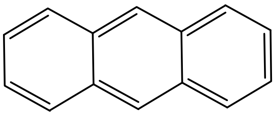
1. Only one of the following molecules is aromatic. Label it **aromatic**.

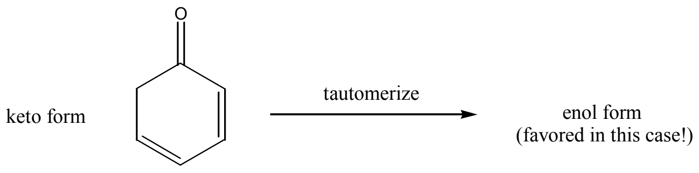
2. Indicate the largest aromatic ring in each of the following aromatic molecules.



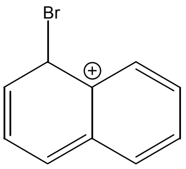



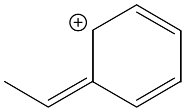
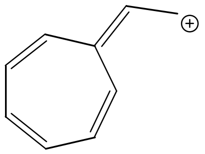




3. Draw the enol form of the following ketone, and construct an explanation for why the enol form is favored in this special case. (Recall that normally the keto form is lower in potential energy and therefore favored.)

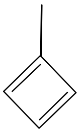
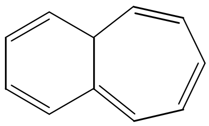
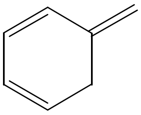
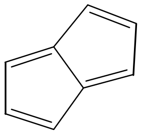
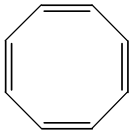
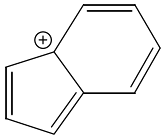


4. For a set of resonance structures, the members of the set that are aromatic are considered lower-potential-energy arrangements of the electrons. These aromatic resonance structures are therefore considered "more important" than their non-aromatic counterparts. For each of the following, draw all important resonance structures, and mark the ones that are more important (aromatic).

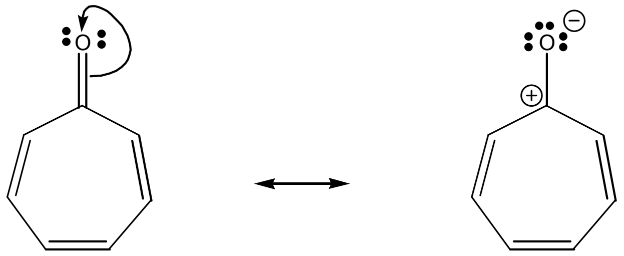


5. Explain why each of the following structures (as shown) is NOT aromatic.

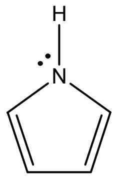
6. The following ketone has a large amount of + charge on carbon and – charge on oxygen. This is because the so-called zwitterionic form of the ketone is much more favorable than you might expect given that it is charged. (A zwitterion is a compound with both a + and a – charge.) Construct an explanation for why the compound has a large amount of zwitterionic character.



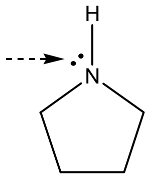
neutral state

zwitterion state preferred

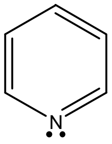
7. The molecule on the left has a lone pair that resides in a *p* orbital despite the fact that in a *p* orbital the lone pair resides closer (90° vs. 109.5°) to N-H and N-C sigma-bonding electrons. Construct an explanation for why this lone pair resides in a *p* orbital.



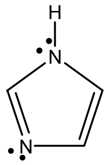
no reason to reside in a *p* orbital so it resides in a sp^3 hybrid orbital



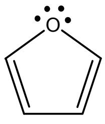
8. Indicate the type of orbital holding each lone pair, and label each molecule that is aromatic.



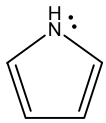
pyridine



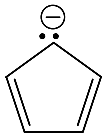
imidazole



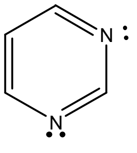
furan



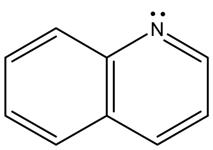
pyrrole



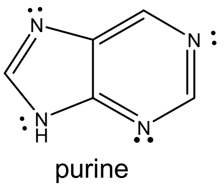
cyclopentadienyl anion (abbreviated "cp")



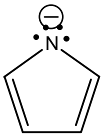
pyrimidine



quinoline



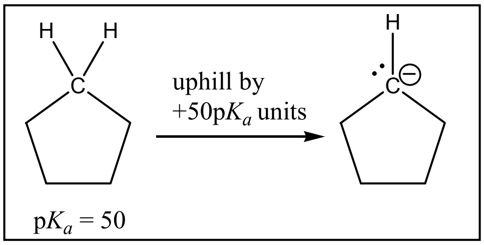
purine

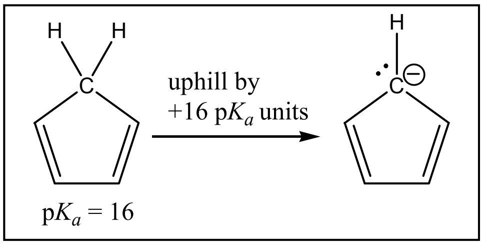


pyrrole anion

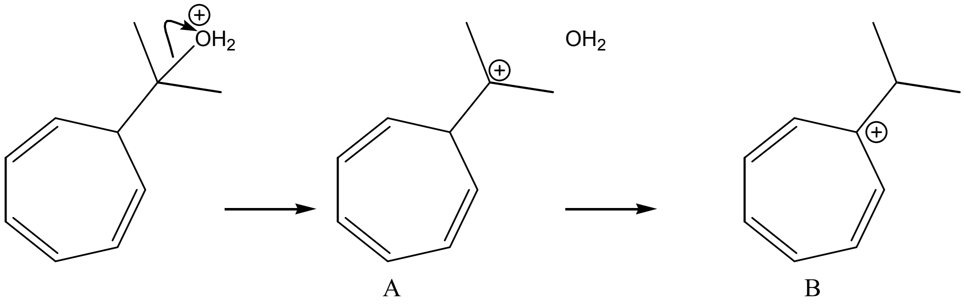
9. All of the "heterocycles" in the previous question are commonly encountered in nature or the laboratory. (A heterocycle is any cyclic molecule containing a noncarbon atom. If you plan to continue your study of organic chemistry beyond this course you may want to familiarize yourself with these common heterocycles.) Construct an explanation for why each of the heterocycles shown above is common.

10. Draw an energy diagram showing both of the following reactions on the same reaction coordinate, and construct an explanation for why the pK_a of cyclopentadiene is much lower than the pK_a of cyclopentane.

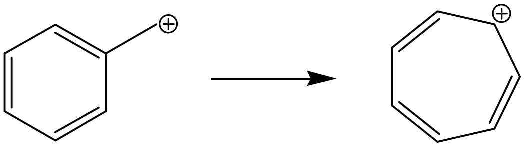




11. Explain why carbocation B is formed preferentially when water leaves. Then use a curved (bouncing) arrow to show the mechanism by which B is formed from A.



12. A benzyl carbocation can rearrange to the ion shown below right (called a tropylium ion).



a. Use curved (bouncing) arrows to show the mechanism of this two-step carbocation rearrangement.

b. What is the driving force for this rearrangement?

13. When an organometallic chemist needs a large anion that will make a strong bond to a metal, a common choice is the anion of pentamethylcyclopentadiene (pentamethylcyclopentadienyl anion).

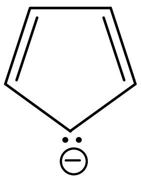
a. Draw pentamethylcyclopentadienyl anion, and explain why it is a stable anion.

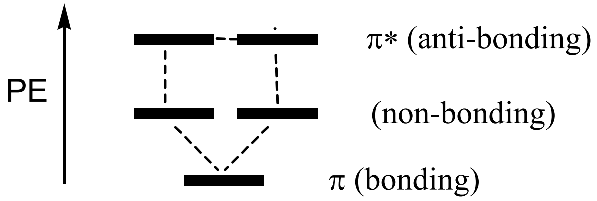
b. Construct an explanation for why pentamethylcyclopentadienyl anion was nicknamed “**cp*.**”

14. Read the assigned pages in the text, and do the assigned problems.

Exercises for Part B

15. The anion below left, has two π bonds that contain four π electrons. Ignore the lone pair on the anionic carbon for now, and place the four electrons from the two π bonds in the MO diagram.





a. According to your MO diagram with four electrons, does this anion have radical character?

b. NOW assume the lone pair on this anion resides in a *p* orbital, and **add two more electrons to your MO diagram** to reflect that the lone pair electrons are part of the π system.

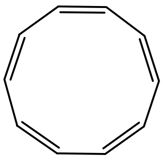
c. Do you expect the lone pair on this anion to reside in a *p* orbital as we assumed in part b? Explain your reasoning.

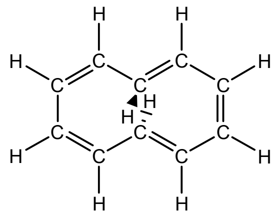
d. Is this cyclic anion expected to be aromatic?

16. Draw an MO diagram for tropylium ion (structure shown on the previous page), and fill in the π electrons showing the ground state of this ion.

17. The first half of Hückels' Rule states that a cyclic conjugated π system with 4n+2 π electrons will be very stable. **A corollary to this rule states that a cyclic conjugated π system with 4n electrons (4, 8, 12, etc.) will be very unstable.** Use MO theory to explain this corollary.

18. Consider two stereoisomers of the 10-member ring shown below.





a. Construct an explanation for why the conformation on the left is very unfavorable.

b. In the conformation on the right, the two H's drawn with wedge-and-dash bonds cause the carbon backbone to flex out of planarity. Do you expect this molecule to be aromatic, anti-aromatic or non-aromatic? Explain.

19. Read the assigned pages in the text, and do the assigned problems.

The Big Picture

This ChemActivity is mostly about recognizing aromatic molecules. As a result there are a large number of exotic aromatic systems shown as examples that you will likely not encounter in other contexts. Most every aromatic molecule we will encounter in this course contains a six-member ring of carbons with three double bonds, a benzene ring (also called a phenyl ring).

The next few activities explore reactions involving aromatic rings. Almost all the examples in these upcoming activities will involve benzene derivatives, but the reactions also apply to larger aromatic molecules and may work with heterocyclic aromatic molecules.

The reactions in the next few ChemActivities are really quite amazing since the key property of benzene and other aromatic molecules is their relative nonreactivity. In fact, the reaction showcased in the next section was discovered accidentally by chemists who were using benzene as a solvent, assuming it was inert (which it usually is).

Common Points of Confusion

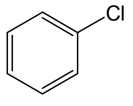
- There are many ways to represent benzene. Unfortunately, the two most common ways (a hexagon with a circle in it or using only one of the two resonance structures) are both a bit misleading.
- Look out for the hexagon with a circle in it representation shown in CTQ 1, and remember that the circle in the middle should really be a dotted-line to properly show that it represents a composite of both of benzene's two equivalent resonance structures. The one good thing about this representation is that it emphasizes the symmetrical nature of benzene.
- If you see benzene represented as one of the two equivalent resonance structures (a six-member ring with three double bonds), remember that benzene is actually symmetrical. Each of the carbon-carbon bonds in benzene is halfway between a single bond and a double bond (a 1-½ bond).
- Much student confusion revolves around anti-aromaticity. This is ironic because it is a rarely encountered phenomenon. One misconception is that an anti-aromatic molecule must violate all the rules of aromaticity. WRONG. An **anti-aromatic** molecule must OBEY all the rules of aromaticity EXCEPT the $4n + 2$ rule. (It must instead have $4n$ π electrons.)
- Students sometimes get confused between the terms anti-aromatic and **non-aromatic**. They are very different. Most molecules are non-aromatic, including all noncyclic molecules. Anti-aromatic molecules turn out to be very rare because it is very easy for most cyclic molecules to violate the planarity required for anti-aromaticity by adopting a nonplanar conformation. This makes them non-aromatic instead of anti-aromatic. In fact, most examples of anti-aromatic molecules contain a **cyclobutadiene** group. This is because, unlike larger rings, the four-atom-ring of cyclobutandiene is unable to twist out of a planar conformation. (Model sets show this well if you are able to make a model of a four-member ring.)
- A lone pair on an aromatic ring resides in a *p* orbital only if doing so makes the molecule aromatic. This is because there is an energy "cost" of putting a lone pair in a *p* orbital vs. a hybrid orbital due to the fact that *p* orbitals are closer to other orbitals than hybrid orbitals (which are, by definition, maximally spread out).

Nomenclature Worksheet 3

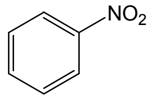
BENZENE DERIVATIVES

Model 1: Naming Mono-Substituted Benzene Rings

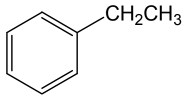
Simple mono-substituted benzene rings can be named by placing the substituent name in front of benzene →



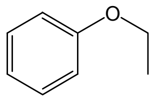
chlorobenzene



nitrobenzene



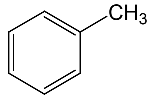
ethylbenzene



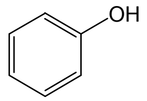
ethoxybenzene

Memorization Task NW3.1: Parent Names of Common Benzene Derivatives

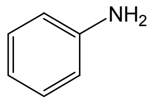
A handful of these are so common that they constitute their own parent name. Know the following…



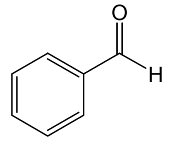
toluene



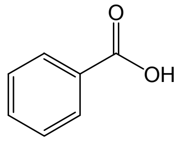
phenol



aniline



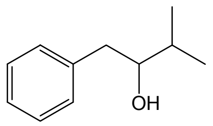
benzaldehyde



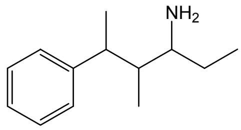
benzoic acid

When a substituent contains an alcohol (OH), amine (NH_2), or in some cases a carbonyl, the substituent is considered the parent chain, and the ring is considered an attached group called a **phenyl group**.

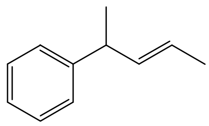
For other functional groups (e.g., alkenes, halogens, etc.) the benzene ring is often the parent chain.

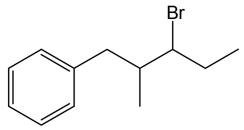


3-methyl-1-phenylbutan-2-ol



4-methyl-5-phenylhexan-3-amine

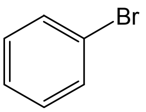

(*E*)-pent-3-en-2-ylbenzene

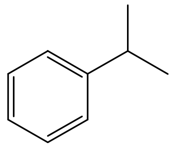


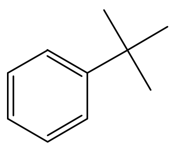
(3-bromo-2-methylpentyl)benzene

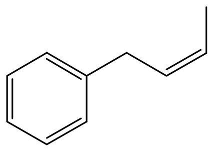
Critical Thinking Questions

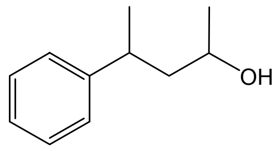
1. (E) What is the name most often used for aminobenzene?
2. Name each of the following compounds.









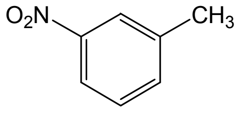


3. Draw each of the following compounds from their names.

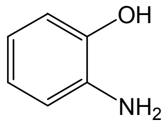
a. 4-phenylbutan-2-ol
b. pent-3-yn-2-ylbenzene
c. (E)-4-phenylbut-3-en-2-ol

Model 2: Naming Multi-Substituted Benzene Rings

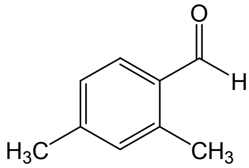
Either the *ortho/meta/para* system or the numbering system may be used for naming benzene rings with two substituents. When there are three or more substituents the numbering system must be used.



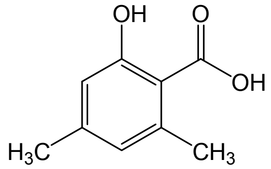
3-methyl-1-nitrobenzene
or
meta-nitrotoluene
or
3-nitrotoluene



2-aminophenol
or
ortho-aminophenol
or
ortho-hydroxyaniline, etc.



2,4-dimethylbenzaldehyde



2-hydroxy-4,6-dimethylbenzoic acid

Note that *ortho, meta,* and *para* are often abbreviated *o, m,* and *p,* respectively.

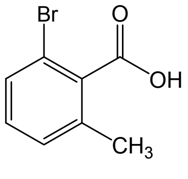
Critical Thinking Questions

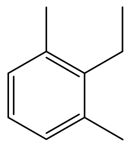
4. Write another name (not appearing in Model 2) for 2-aminophenol.

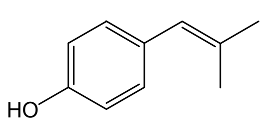
5. Draw the structure that corresponds to the name 2-phenyl-6-methylphenol.

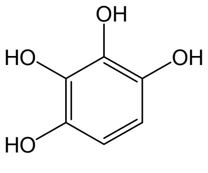
6. Explain why the following is not a correct name, 4,5-dimethylphenol.

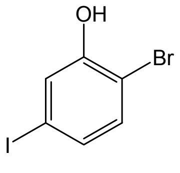
7. Name each of the following compounds.









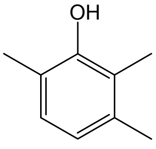


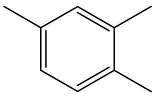
8. Draw each of the following compounds from their names.

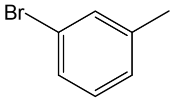
a. *p*-benzenediol
b. 2,4,6-trinitrotoluene
c. (E)-*ortho*-(prop-1-enyl)phenol

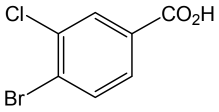
Exercises

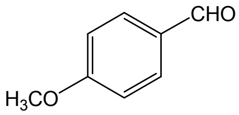
1. Name each of the following compounds.

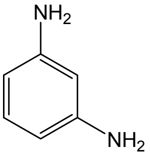


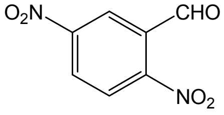


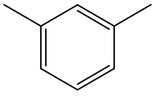


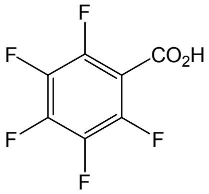


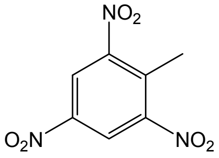












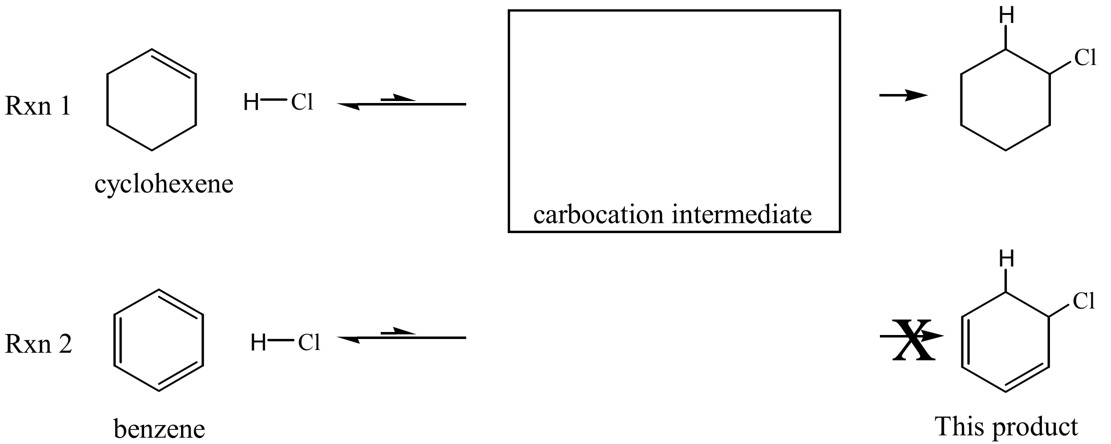
2. Draw each of the following compounds from their names.
   a. *o*-nitroaniline
   b. 4-aminobenzaldehyde
   c. *para*-hydroxybenzoic acid
   d. *o*-methyltoluene (also called *ortho*-xylene or *o*-xylene)
   e. *meta*-xylene
   f. *p*-xylene
   g. *m*-propoxynitrobenzene
   h. 2,3-dibromophenol
   i. 2,4,5-trimethylaniline
   j. 2,6-dimethoxybenzaldehyde

ChemActivity 19: EAS

PART A: ELECTROPHILIC AROMATIC SUBSTITUTION (EAS)

(What products are formed when a strong electrophile is added to benzene?)

Model 1: (review) Electrophilic Addition of HCl



This product **DOES NOT** form!

Critical Thinking Questions

1. For Rxn 1 (above) draw curved arrows showing the mechanism of electrophilic addition of HCl. Include an appropriate carbocation intermediate in the box above.

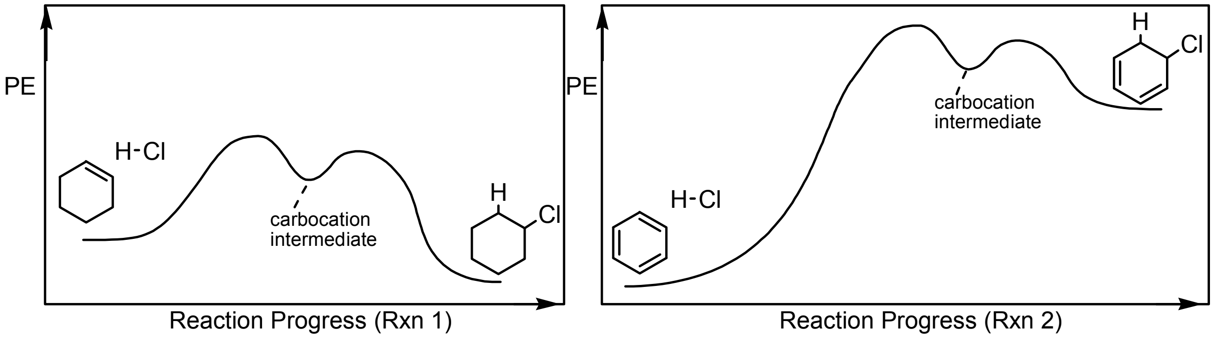


Figure 19.1: Reaction Diagrams for Electrophilic Addition of HCl

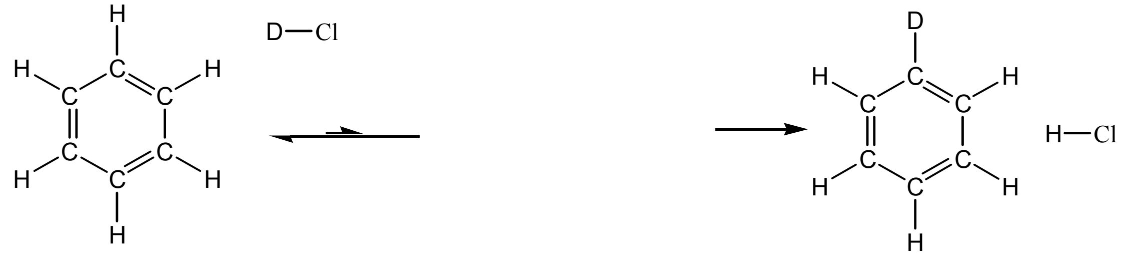
2. Rxn 1 is slightly downhill. Rxn 2 is very uphill (*see* Figure 19.1). Construct an explanation for why the reactants in Rxn 2 are much lower in P.E. than the products.

3. Draw the carbocation that would form in Rxn 2, and explain why this carbocation goes back to the starting material (H–Cl and benzene) instead of forming the product.

Model 2: Electrophilic Aromatic Substitution (EAS)

- Recall that deuterium (D) has nearly identical reactivity as hydrogen (H).
- In the following reaction, assume D–Cl reacts the same way as would H–Cl.
- When benzene is treated with D–Cl, one H is replaced with a D. (With excess D–Cl this continues until all the H's have been replaced and the product is C_6D_6.

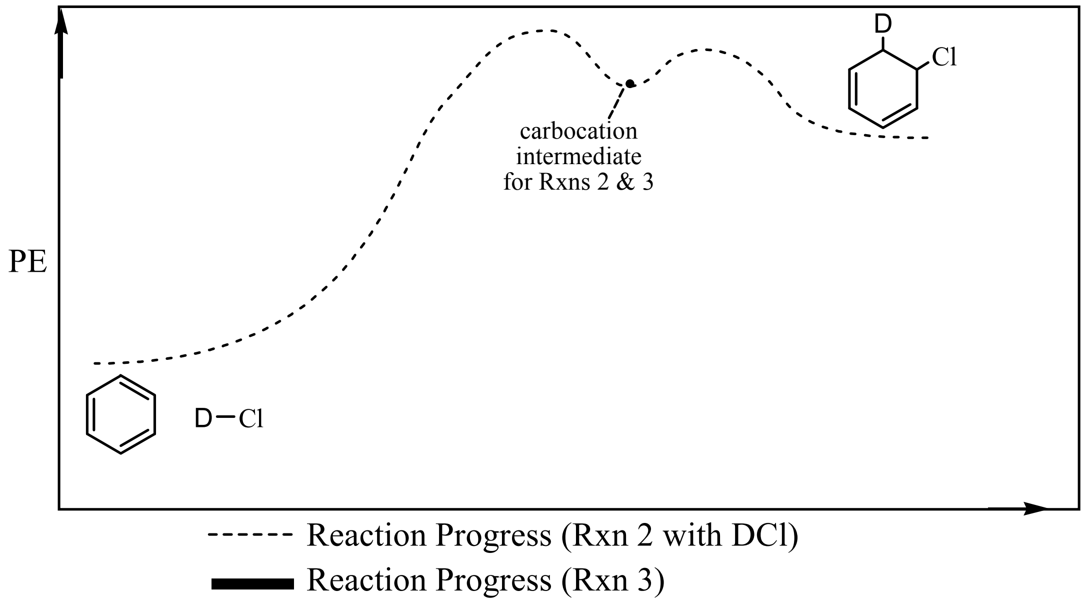
Rxn 3



Critical Thinking Questions

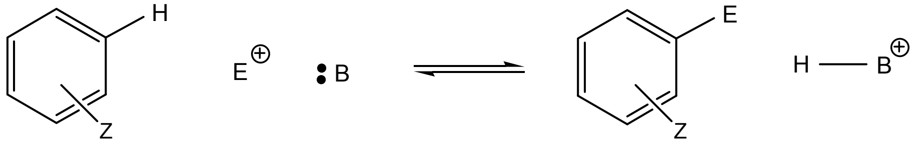
4. Use curved arrows to show a reasonable mechanism for Rxn 3 in Model 2. (*Hint*: The first step is formation of a carbocation intermediate, just as in Rxn 2.)

5. Rxns 2 and 3 have the same starting materials and carbocation intermediate, but different products. The energy diagram for Rxn 2 (using DCl in place of HCl) is shown below using a *dotted line.* On this same set of axes, draw a **solid line** showing the progress of Rxn 3.



6. Construct an explanation for why Rxn 3 is much more likely to occur than Rxn 2. (Note: Rxn 2 does not occur under normal circumstances.)

7. Draw a generalized mechanism for EAS (Electrophilic Aromatic Substitution) showing the substitution of an electrophile (E^+) for one of the H's of benzene in the presence of a mild base (:B). (Note: In Rxn 3, $E^+ = D^+$, and :B = Cl^-)



Model 3: Lewis Acid Catalysts

Many EAS electrophiles must be made *in situ* (in the reaction mixture). For example: $^+NO_2$ is made when sulfuric acid protonates (adds H^+ to) nitric acid. (The mechanism for this is in your homework exercises.)

EAS reactions including Synthetic Transformations 19.4-19.6 (on the next page) require a **Lewis acid catalyst** to generate the electrophile. (Recall that an electron-deficient species can be called a Lewis acid.)

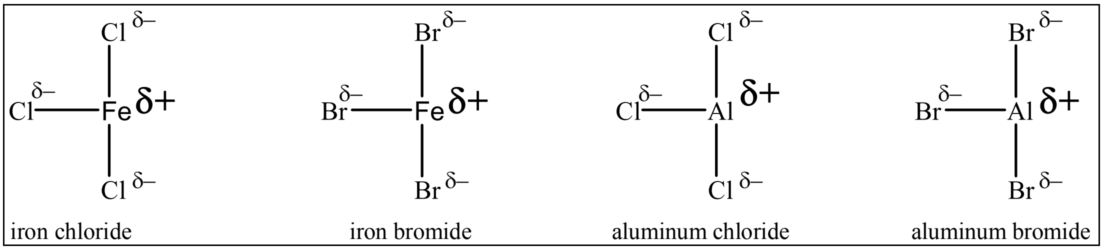


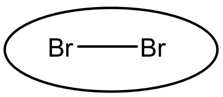
Figure 19.2: Lewis acid catalysts used for Synthetic Transformations 19.4-19.6

Critical Thinking Questions

8. Confirm that each atom shown in Figure 19.2 has a zero formal charge.
   a. Do the partial charges shown fit the electronegativity data in Model 3 of ChemActivity **4**?
   b. Based on the partial charges shown, mark the atom on each catalyst that is most Lewis acidic.

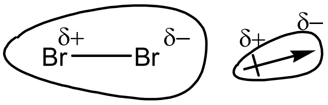
9. To the structure of Br_2 bound to $FeBr_3$ (below, far right), add a drawing of the electron cloud of Br_2 (and appropriate partial charges). **DO NOT** attempt to draw the electron cloud of $FeBr_3$.

Outline of Undisturbed Electron Cloud of Br_2



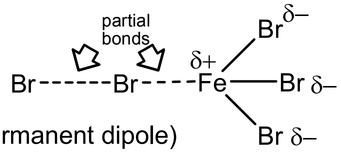
(no dipole)

Outline of Electron Cloud of Br_2 near polar molecule



(induced dipole)

Br_2 with partial bond to $FeBr_3$ (outline of electron cloud not shown)

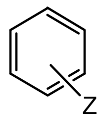
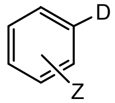
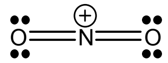
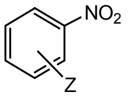
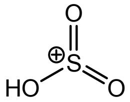
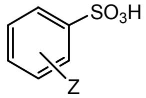
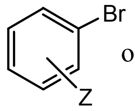
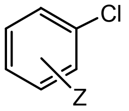
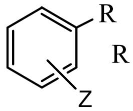
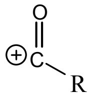
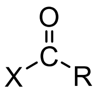
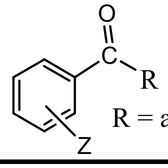


(permanent dipole)

10. Circle the most electrophilic Br atom above. Note the formal charge is misleading in this case.

11. Explain why benzene does not undergo EAS with Br_2 unless $FeBr_3$ (or another Lewis acid catalyst) is present.

Synthetic Transformations 19.1-19.6: EAS Reagents (table)

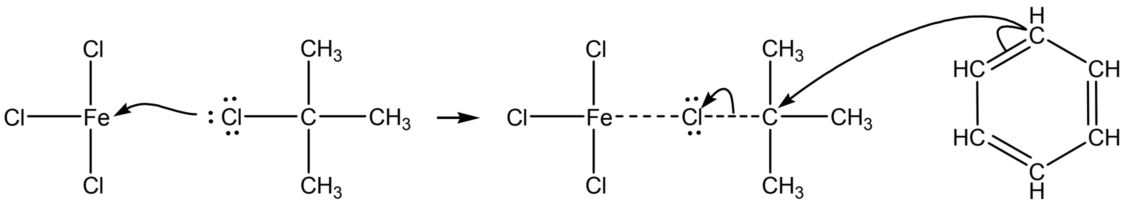
Reactant	Synth. Transf.	Electrophile (E^+)	Reagents	Product/s
 benzene when Z = H	**19.1**	$D^{\oplus}$	Any deuterated strong acid	
	19.2		H_2SO_4 and HNO_3	
	19.3		anhydrous sulfuric acid (H_2SO_4 with no water)	
	19.4	$Br^{\oplus}$ or $Cl^{\oplus}$	Br_2 and $FeBr_3$ or Cl_2 and $FeCl_3$	 or 
	19.5	$R^{\oplus}$	R-X, AlX_3 (X = Cl or Br)	 R = alkyl group
	19.6		 AlX_3 (X = Cl or Br)	 R = alkyl group

Memorization Task 19.1: Use $FeBr_3$ with Br_2; $FeCl_3$ with Cl_2; $AlBr_3$ with RBr; etc.

For the reactions above, the halogen in the reagent (e.g. R—Br) should be matched to the halogen in the Lewis acid catalyst (e.g. $AlBr_3$).

Critical Thinking Questions

12. Complete the following mechanism and show the end product.

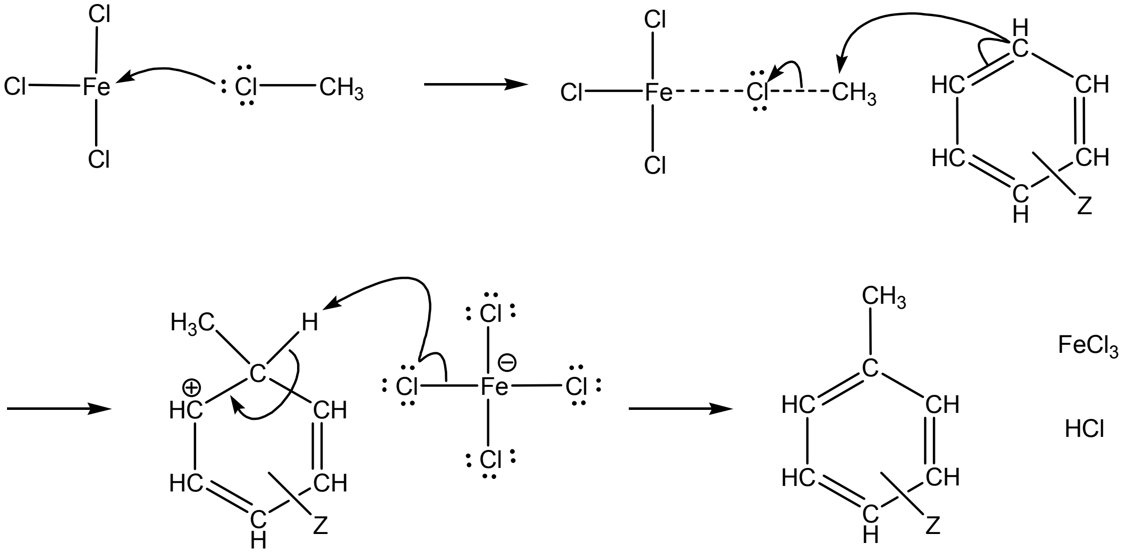


13. For Synthetic Transformation 19.4, you MUST follow the rule in Memorization Task 19.1 or an unwanted side product will result. Draw the unwanted side product that results if you attempt to transform benzene into chlorobenzene using $Fe\underline{Br}_3$ and $\underline{Cl}_2$.

PART B: DIRECTING EFFECTS OF ELECTRON-DONATING GROUPS

(In an EAS reaction involving methylbenzene (toluene), where on the ring will the electrophile appear?)

Model 4: (*Review*) Mechanism of EAS with Benzene



Note: The **Z** group replaces an unspecified H on the aromatic ring

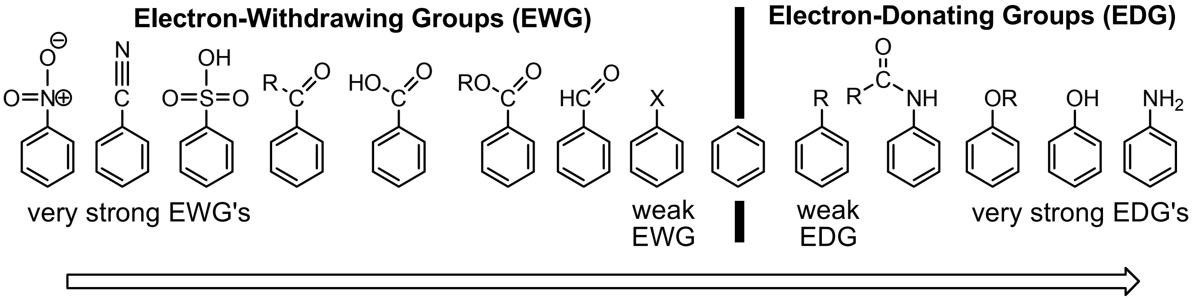
Critical Thinking Questions

14. Explain why $FeCl_3$ is considered a catalyst in the EAS reaction in Model 4.

15. In an EAS reaction, is the π bond of the aromatic ring acting as a **nucleophile** or **electrophile**? (Circle one and explain your reasoning.)

16. Which do you expect to be faster, an EAS reaction in which the "Z" group is an **Electron-Withdrawing Group (EWG)** or an **Electron-Donating Group (EDG)**? Explain your reasoning.

Model 5: Electron-Withdrawing and Electron-Donating Groups


Electron-Withdrawing Groups (EWG)
Electron-Donating Groups (EDG)
very strong EWG's
weak EWG
weak EDG
very strong EDG's

Critical Thinking Questions

17. (Check your work) Is your answer to the previous question consistent with the fact that an EAS reaction involving nitrobenzene (C_6H_5—NO_2) is much slower than an EAS reaction involving benzene (C_6H_6)?

18. Draw the structure of a benzene derivative that is expected to undergo an EAS reaction FASTER than benzene itself.

19. The arrow at the bottom of Model 5 can represent the relative speed of an EAS reaction. Write "Slow EAS" at the appropriate end of the arrow and "Fast EAS" at the other end.

20. (Check your work) Write "Deactivated Rings" above the EWG's and "Activated Rings" above the EDG's, and check to make sure this is consistent with your answer to the previous question.

21. Answering the following questions will help you recognize EWG's and EDG's.
    a. Circle each π bond, and add each lone pair to the structures in Model 5.
    b. Confirm that each electron-withdrawing group (EWG) listed (except for the weakest EWG) has a π bond next to the aromatic ring.
    c. Confirm that each electron-donating group (EDG) listed (except the weakest EDG) has a lone pair on the atom next to the aromatic ring.

Memorization Task 19.2: Recognizing EWG's and EDG's

Electron-withdrawing groups (EWG's) usually have a π bond next to the aromatic ring.

Electron-donating groups (EDG's) usually have a lone pair on the atom next to the aromatic ring.

The main exceptions are halogens (which are weak EWG's), and alkyl groups (which are weak EDG's).

Mem. Task 19.3: A ring with a strong EWG will not undergo a Friedel-Crafts reaction

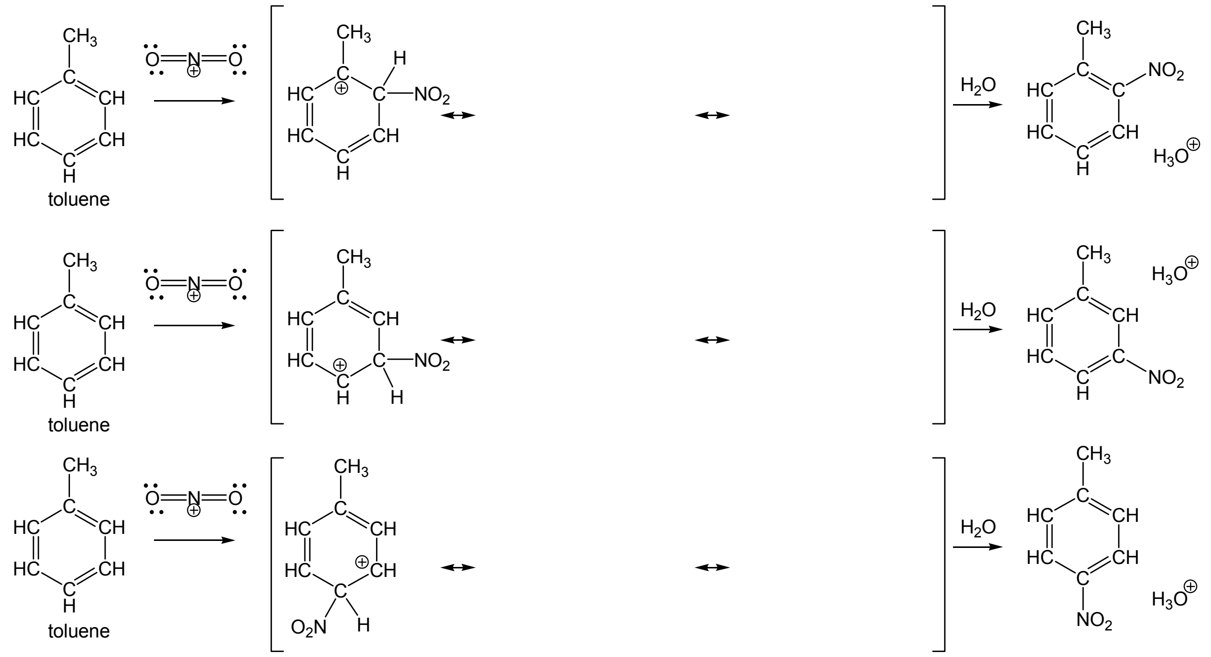
Synthetic Transformations 19.5 and 19.6 are called "**Friedel-Crafts alkylation**" and "**Friedel-Crafts acylation**" after their inventors, Charles Friedel and James Crafts. (An **acyl group** is an RC=O group).

Aromatic rings with strong electron-withdrawing groups do not yield good results in these reactions.

Critical Thinking Questions

22. Go back to Part A and label Synthetic Transformations 19.5 and 19.6 "**Friedel-Crafts alkylation**" and "**acylation**," respectively, and make a note that neither works with a deactivated ring.

Model 6: Electrophilic Aromatic Substitution with Toluene



Memorization Task 19.4: ortho, meta, para nomeclature for substituents on a benzene ring

Two groups attached to adjacent benzene-ring carbons (e.g. C_1 and C_2) are ***ortho*** to each other.
Two groups attached one carbon apart on a benzene ring (e.g. C_1 and C_3) are ***meta*** to each other.
Two groups attached two carbons apart on a benzene ring (e.g. C_1 and C_4) are ***para*** to each other.

Critical Thinking Questions

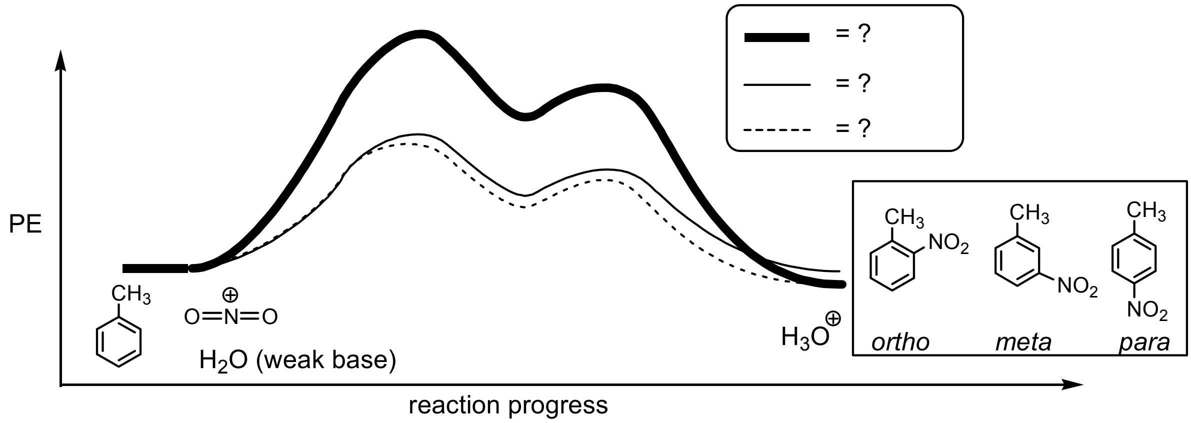
23. (E) Label the three different nitrotoluene products in Model 6 using the names *ortho*-nitrotoluene, *meta*-nitrotoluene, and *para*-nitrotoluene according to the definitions above.

24. Add curved arrows showing the movement of electrons in all three reactions above.

    a. For each carbocation, draw the other two important resonance structures (r.s.).

    b. Confirm that the carbocation leading to the *meta* product has three equivalent resonance structures. In contrast, the *ortho* and *para* carbocations have **one r.s. that stands out as more important**. Circle these more important resonance structures, and explain your reasoning.

25. The following energy diagram shows pathways to the ***ortho, meta,*** and ***para*** products.



a. Label the pathway corresponding to the ***meta*** product, and explain your reasoning.

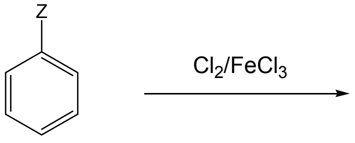
b. When toluene is mixed with nitric acid and sulfuric acid (giving $^{+}NO_2$) two of the three products in the box above are formed. Circle these two, cross out the one that is not observed in significant quantities, **and explain your reasoning**.

c. (Check your work) The carbocations leading to the *ortho* and *para* products are very similar. In what way are these two sets of resonance structures similar?

d. Look closely at the *ortho* and *para* intermediates (or products). One is slightly lower in potential energy due to steric effects. Which one? ***ortho*** or ***para*** (circle one).

e. In an EAS reaction starting with toluene, the CH_3 group is said to be functioning as an "**ortho and para director**." Construct an explanation for this terminology.

f. In this course we will also encounter "**meta directors**." Draw the major product of the hypothetical reaction at right if you assume the "Z" group is a *meta* director.



Memorization Task 19.5: Activators = *o/p* Directors; Deactivators (usually) = *m* Directors

For reasons we will explore throughout the rest of this activity:

- all **activators** (electron-donating groups) are *ortho* and *para (o/p)* directors
- all **deactivators** (electron-withdrawing groups) EXCEPT HALOGENS are *meta (m)* directors

Halogens are the exception (again). They are the only deactivators that are o/p directors. We will explore why later.

Critical Thinking Questions

26. (Check your work) On the previous page it says that a methyl group is an *o/p* director. Does this fit with where an alkyl (R) group is found on the chart in Model 5? Explain.

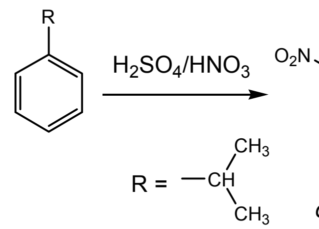
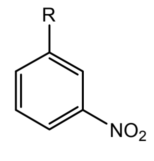
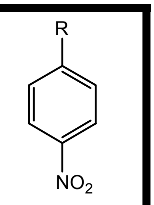
27. Add the headings "***o/p* directors**" and "***m* directors**" to appropriate sides of the chart in Model 5.

Model 7: Steric vs. Electronic Effects in EAS

For the reaction below, chemists say the ***meta* product is NOT formed because of unfavorable electronic effects**. (That is, the *ortho* and *para* carbocation intermediates have more tertiary character.)

Though electronic effects (e.g. carbocation stability) are generally stronger than steric effects, **steric effects** *can* have an impact.

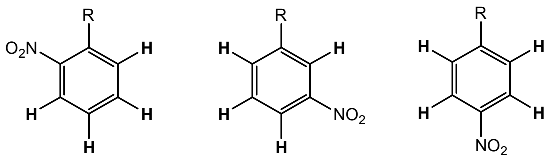
For example: If the R group at right is large enough *para* is favored over *ortho*.

 *ortho* (13 %)	 *meta* (<2 %)	 *para* (85 %)
R = $-CH_3$ *ortho* (63 %)	*meta* (<2 %)	*para* (35 %)

Critical Thinking Questions

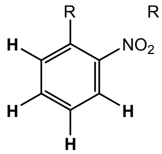
28. Explain the very strong preference for the *para* product when R = isopropyl (as compared to when R = methyl).

29. Explain the statement: "Without steric effects, one would expect the *ortho* product of this reaction to be exactly twice as abundant as the *para* product." (If you are stuck, *see Hint* below.)



ortho (66 %) *meta* (~0 %) *para* (33 %)

Expected Ratio if there were no Steric Effects



R = alkyl group

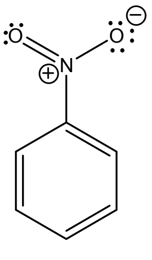
Hint: What is the difference between this product and the *ortho* structure in the box at left?

PART C: RESONANCE-WITHDRAWING AND DONATING GROUPS

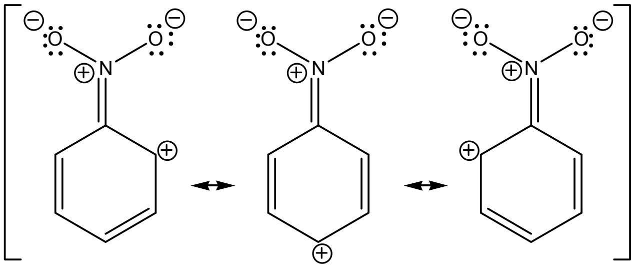
(How do resonance-withdrawing and donating groups affect rate and placement in EAS?)

Model 8: Second-order Resonance Structures

Second-order resonance structures are like "**assistant resonance structures**." They are not as important as regular (first-order) resonance structures, but can help us make predictions in certain instances.



Nitrobenzene



Second-Order Resonance Structures of Nitrobenzene

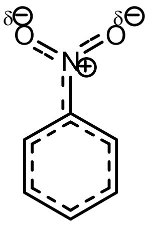
Critical Thinking Questions

30. Explain why the three **second-order resonance structures** shown in Model 8 are NOT considered “important” resonance structures. That is, why are they "not as important" as a regular, first-order resonance structure such as the one at the far left of Model 8? (*Hint*: Count formal charges.)

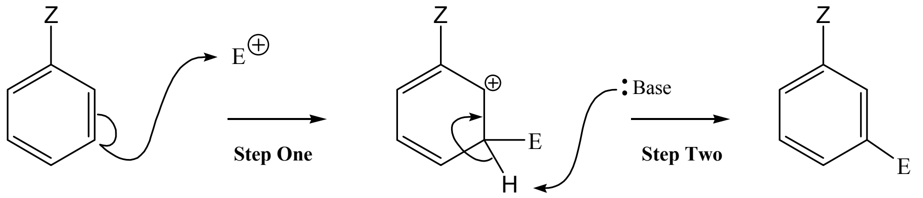
31. Add curved arrows to nitrobenzene at the top of the page showing how you would change it into one of the second-order resonance structures. Then use curved arrows to generate each of the subsequent second-order resonance structures.

32. The second-order resonance structures of nitrobenzene tell us that the nitro group generates partial positive charge at certain carbons on the aromatic ring. Complete the composite drawing of nitrobenzene below by placing a δ+ on appropriate carbons in the ring.

Composite Drawing of Nitrobenzene
(a combination of all first- and second-order resonance structures)



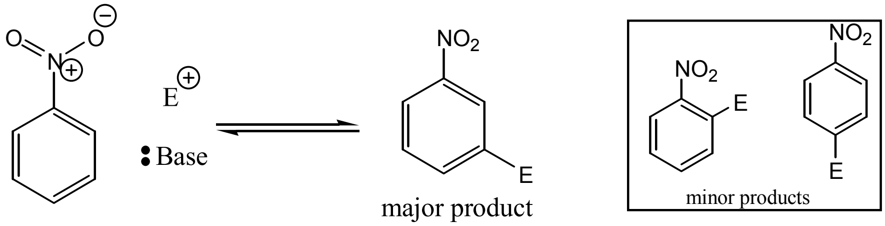
33. (*Review*) In the first step of an electrophilic aromatic substitution (EAS) reaction **the aromatic ring is acting as a nucleophile** and reacting with the electrophile (E$^+$).



a. Which is more likely to react with an electrophile, **a carbon that is electron-rich**, or **a carbon that is electron-poor and holds a $\delta+$ charge** (circle one)?

b. Assume that Z = nitro group and add $\delta+$ charges to appropriate ring carbons according to your answer to the CTQ at the bottom of the previous page.

c. Construct an explanation for why this reaction yields ***meta*** **as the major product**.



Term Introduction: Resonance vs. Inductive withdrawing/donating groups

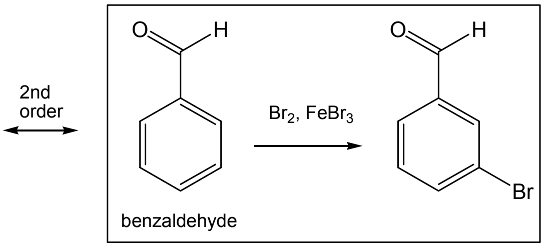
Resonance electron-withdrawing (or donating) group = group that withdraws or donates electrons via π bonds as demonstrated by 2nd order resonance structures (e.g. NO_2) — usually a **STRONG** effect.

Inductive electron-withdrawing (or donating) group = group that withdraws or donates electrons only via inductive effects (e.g. an alkyl group). This is a relatively **weak** effect.

Memorization Task 19.6: Identifying Resonance Electron-withdrawing Groups

A group with a π bond next to an aromatic ring will be a resonance electron-withdrawing group

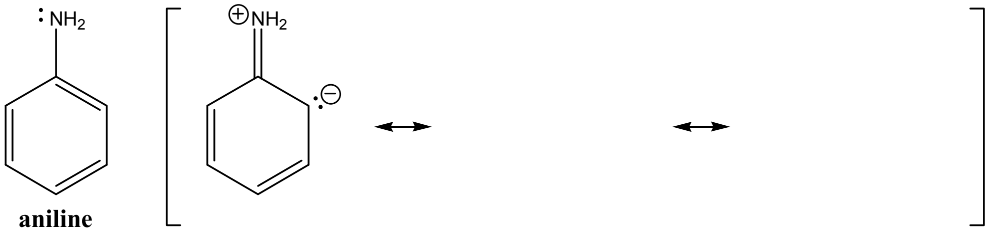
34. Draw second-order resonance structures of the aromatic starting material (benzaldehyde) that can be used to justify why the EAS reaction in the box yields mostly *meta*-bromobenzaldehyde.



(Note that a more complete explanation for why the meta product is preferred must address the relative energies of the carbocation intermediates. Questions that focus on this issue can be found in the Exercises for this ChemActivity.)

35. Draw examples of two mono-substituted benzene rings (other than nitrobenzene and benzaldehyde) that also are expected to preferentially direct an electrophile to the *meta* position.

36. Add curved arrows to aniline showing how to generate the second-order resonance structure shown. Then use curved arrows to generate the two missing second-order resonance structures.

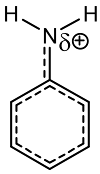


aniline

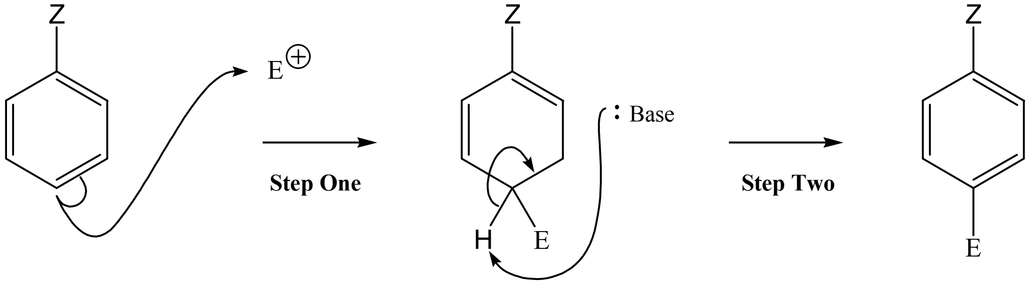
Second-Order Resonance Structures for Aniline

37. Complete the composite drawing of aniline at right by placing a δ– on appropriate carbons in the ring.

Composite Drawing of Aniline (showing a combination of all first- and second-order resonance structures)

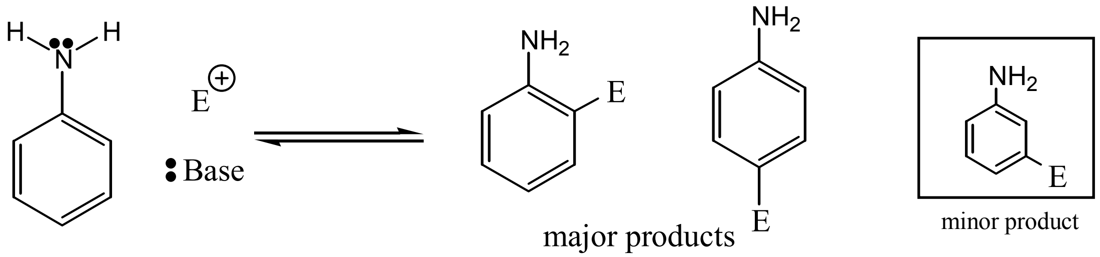


38. Recall that, in the first step of an EAS reaction, **the aromatic ring is acting as a nucleophile** and reacting with the + charged electrophile (E^+).



a. Assume that Z = an amino group (NH_2), and add δ– to appropriate ring carbons on the structure of the starting material above according to your answer to the previous CTQ.

b. Construct an explanation for why, when Z = NH_2, the major products are ***ortho*** and ***para***.



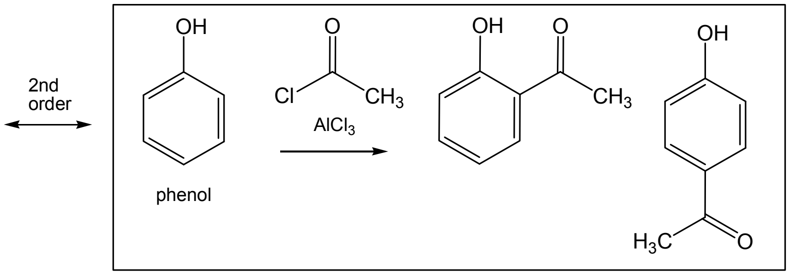
major products

minor product

Memorization Task 19.7: Identifying Resonance Electron-donating Groups

An atom with a lone pair next to an aromatic ring will function as a resonance electron-donating group

39. Draw second-order resonance structures of the aromatic starting material (phenol) that can be used to justify why the EAS reaction in the box yields mostly the *ortho* and *para* products.

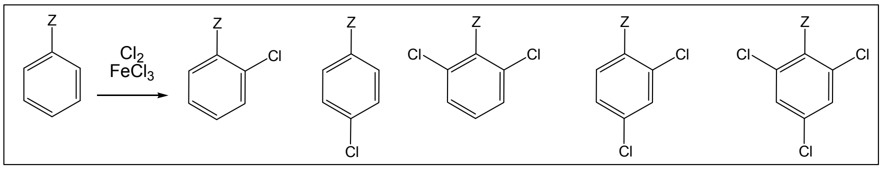


(Note that a more complete explanation for why the ortho and para products are preferred must address the relative energies of the carbocation intermediates. Questions that focus on this issue can be found in the Exercises for this ChemActivity.)

40. Draw examples of two mono-substituted benzene rings (other than aniline and phenol) that also are expected to preferentially direct an electrophile to the *ortho* and *para* positions.

41. As stated earlier, resonance electron-withdrawing and donating effects are strong in comparison to other effects (e.g. steric or inductive effects). Circle the answer that completes the sentence…
    a. A resonance electron-withdrawing group is a strong ***ortho/para*** **director** or ***meta*** **director**.
    b. A resonance electron-donating group is a strong ***ortho/para*** **director** or ***meta*** **director**.

42. Which identity of Z is expected to give a higher yield of the di-chloro and tri-chloro products shown below: **Z = CH_3** or **Z = OH**? (Circle one and explain your reasoning.)



Memorization Task 19.8: EAS with an activated ring often results in multiple substitutions

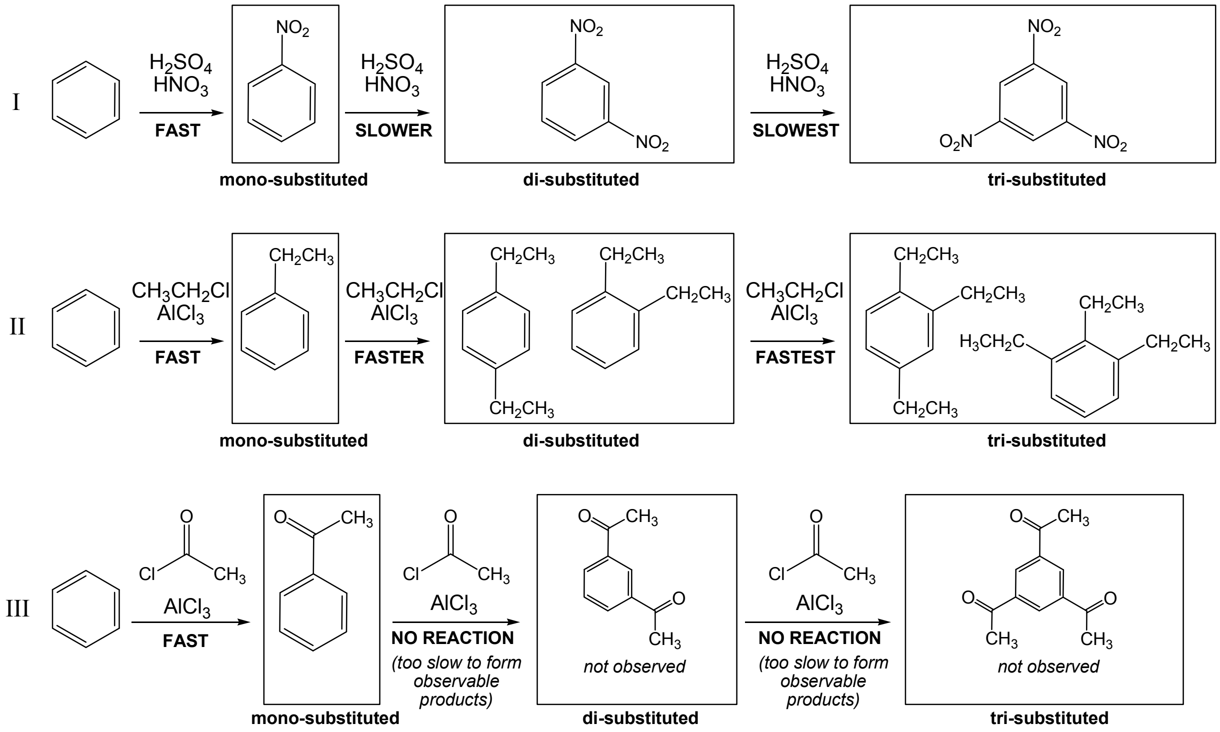
EAS reactions in which the ring has one or more strong electron-donating groups (= resonance electron-donating groups) often result in products with more than one electrophile on the ring. As we will see in the next section, this is especially true for Friedel-Crafts alkylations, (but *not* F-C acylations)!!

43. (Check your work) Is your answer to the previous question consistent with Mem. Task 19.8?

PART D: FRIEDEL-CRAFTS (SPECIAL CONSIDERATIONS)

(What are the limitations of Friedel-Crafts reactions?)

Model 9: Polysubstitution in Friedel-Crafts Alkylations

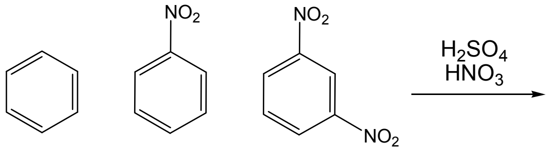


Critical Thinking Questions

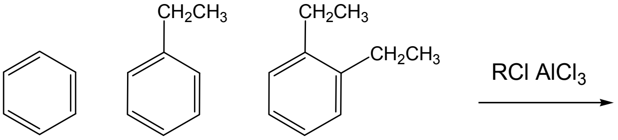
44. (*Review*) Explain why the second reaction in **Reaction Sequence I** is slower than the first reaction.

45. (*Review*) Explain why the second reaction in **Reaction Sequence II** is faster than the first reaction.

46. Consider a hypothetical solution consisting of one molecule of benzene, one molecule of nitrobenzene, and one molecule of dinitrobenzene. If you treat this mixture with one molecule of an electrophile (e.g. H_2SO_4/HNO_3), which ring (**benzene, nitrobenzene,** or **dinitrobenzene**) is most likely to react with the single $^+NO_2$ electrophile? (Circle one and explain your reasoning.)



47. Consider a hypothetical solution consisting of one molecule of benzene, one molecule of ethylbenzene, and one molecule of diethylbenzene. If you treat this mixture with one molecule of electrophile (e.g. R—Cl/$AlCl_3$), which ring (**benzene, ethylbenzene,** or **diethylbenzene**) is most likely to react with the single R^+ electrophile? (Circle one and explain your reasoning.)



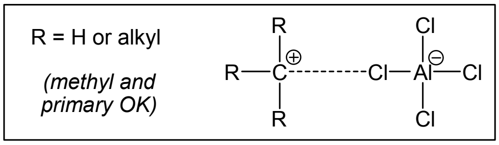
48. For **Reaction Sequence II** in Model 9, if you mix equal amounts of benzene and electrophile (e.g. CH_3CH_2Cl + $AlCl_3$ catalyst) you obtain mostly the di- and tri-ethyl products shown in **Reaction Sequence II** and very little of the mono-ethyl product (ethylbenzene). Explain.

49. In contrast, for **Reaction Sequence III**, if you mix equal amounts of benzene and electrophile you will isolate only one of the products shown in **Reaction Sequence III**. Circle the single product formed and explain why *only* this product is formed.

50. (Check your work) Is the underlined statement in **Memorization Task 19.8** consistent with your conclusions regarding **Reaction Sequences I** to **III** in Model 9?

Model 10: Carbocation Rearrangement in Friedel-Crafts Alkylation

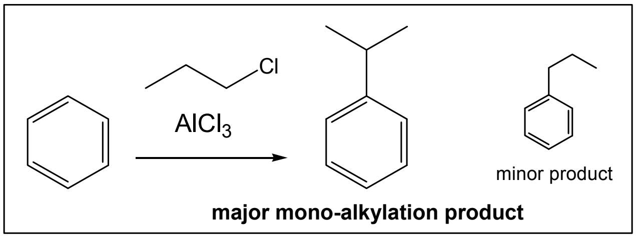
The electrophile in a Friedel-Crafts alkylation is essentially a carbocation. (Note that due to stabilization by $^{-}AlX_4$ it is acceptable to propose a + charge on a methyl or primary carbon in an F-C alkylation).



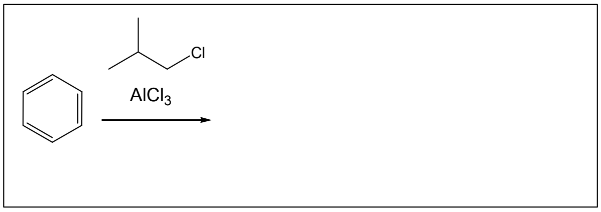
Like ordinary carbocations, Friedel-Crafts alkylation electrophiles will undergo favorable rearrangements.

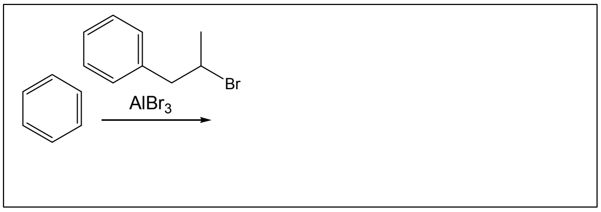
Critical Thinking Questions

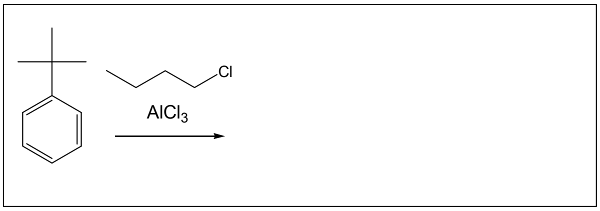
51. Use curved arrows to show the mechanism of formation of the major mono-alkylation product. Show the electrophile as an ordinary carbocation. (i.e., no need to show the $^{-}AlCl_4$ counterion.)

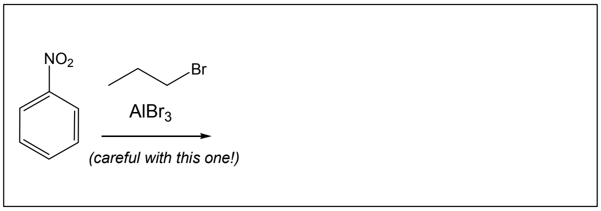


52. For each, assume carbocation rearrangement and draw a likely F-C mono-alkylation product. *(Assume that benzene is in huge excess so that polyalkylation products do not dominate.)*





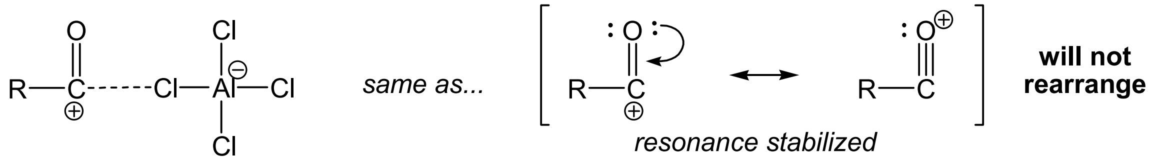




(careful with this one!)

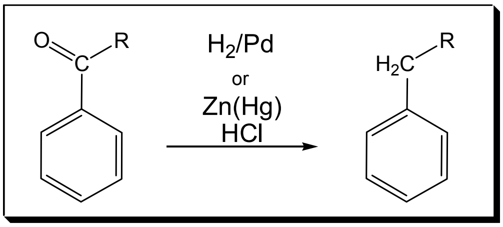
Memorization Task 19.9: F-C acylation not plagued by rearrangement (or polysubstitution)

The electrophile in F-C acylation is stable with respect to rearrangement due to resonance stabilization.



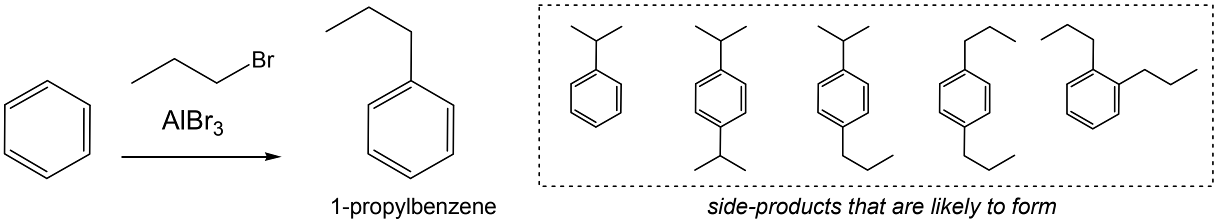
(Recall that **Friedel-Crafts acylation**s also do not suffer from polysubstitution since the first acyl group added to a ring deactivates the ring toward further substitution.)

Synthetic Transformation 19.7: Reduction of a benzyl carbonyl



Note that Zn(Hg)/HCl has no effect on ordinary C=C π bonds.

53. The following synthesis of 1-propylbenzene gives multiple side products. Propose an alternate synthesis from benzene that gives a high yield of the desired product with little or no side products. *(Hint: If you are stuck, see Memorization Task 19.10 on the next page.)*



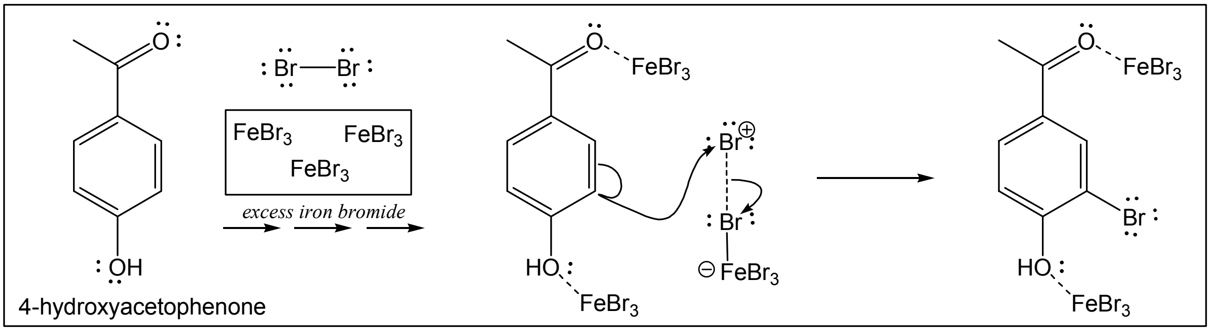
Memorization Task 19.10: F-C acylation (followed by reduction) avoids common problems

Friedel-Crafts alkylations are not usually performed using alkyl halides that are prone to rearrangement because the result is a mixture of products, and thus a low yield of any one particular product. To obtain a single alkylbenzene product, the corresponding **Friedel-Crafts acylation** should be performed, followed by reduction of the carbonyl using H_2/Pd or Zn(Hg)/HCl.

Model 11: How Much Lewis Acid Catalyst Is Needed?

In a standard Friedel-Crafts alkylation, only a small (catalytic) amount of Lewis acid catalyst is needed.

In a reaction in which there are also Lewis bases present (such as any N or O with a lone pair), each Lewis base in solution will bond to a molecule of **Lewis acid catalyst**.



Each Lewis acid catalyst that is bound to a Lewis base is rendered inactive.

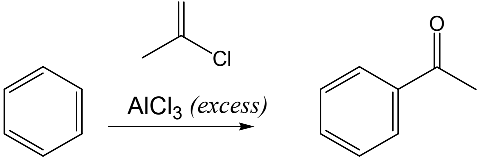
In such situations it is necessary to use a large excess of Lewis acid catalyst—enough to satisfy each Lewis base in solution AND still have free catalyst available to perform the desired EAS reaction.

Critical Thinking Questions

54. Use three curved arrows to show how the three $FeBr_3$ molecules shown in the box in Model 11 become bound to three different lone pairs.

55. (E) Explain why the EAS reaction shown in Model 11 requires more than two times the amount ("> 2 molar equivalents") of $FeBr_3$ compared to the amount of 4-hydroxyacetophenone.

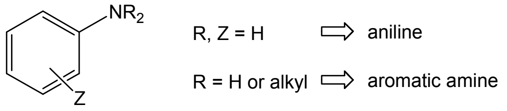
56. Construct an explanation for why all Friedel-Crafts acylations (including the one below) require greater than one molar equivalent of Lewis acid catalyst ($AlCl_3$). That is, what happens to the first molar equivalent of Lewis acid catalyst in a Friedel-Crafts acylation?



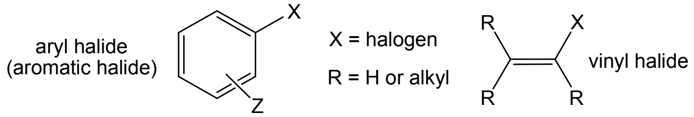
Memorization Task 19.11: Other of Friedel-Crafts limitations

In addition to the limitations outlined in Part D (above), Friedel-Crafts reactions …

- do NOT work with aniline (or any other aromatic amine) as the nucleophile



- do NOT work with an aryl or vinyl halide in place of an alkyl halide (as the electrophile)



PART E: COMPETING EFFECTS AND MULTI-SUBSTITUENT RINGS

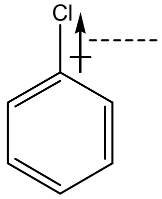
(What happens if you have two substituents on a ring that do not agree in terms of directing effects?)

Model 12: Inductive Effects vs. Resonance Effects

Recall that an **inductive effect** is the donation or withdrawal of electron density through σ bonds (as shown below, left), and…

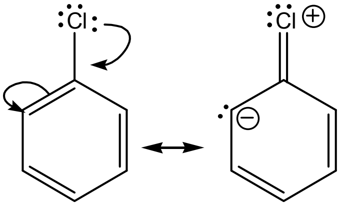
A **resonance effect** is the donation or withdrawal of electron density through π bonds as demonstrated by first- or second-order resonance structures (as shown below, right).

Example of an Inductive Effect



Cl is more electronegative than C, so it inductively withdraws electron density from the ring.

Example of a Resonance Effect



Resonance-donating effects place extra electron density at the *ortho* and *para* positions on the ring.

Recall Memorization Task 19.5 from Part B of this ChemActivity...

Memorization Task 19.5: Activators = *o/p* Directors; Deactivators (usually) = *m* Directors

For reasons we will explore throughout the reset of this activity:

- all **activators** (electron-donating groups) are *ortho* and *para (o/p)* directors in EAS
- all **deactivators** (electron-withdrawing groups) EXCEPT HALOGENS are *m* directors in EAS

Halogens are the exception (again). They are the only EAS deactivators that are o/p directors. We will explore why later.

Critical Thinking Questions

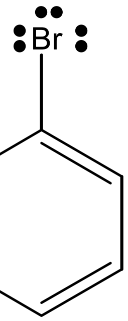
57. (E) According to Memorization Task 19.5, are halogens ***m* directors** or ***o/p* directors** in EAS?
58. According to Memorization Task 19.5, halogens are net EAS deactivators. Based on this and info in Model 12, which is stronger in the case of halogens, **inductive effects** or **resonance effects**? (Circle one and explain your reasoning.)

Memorization Task 19.12: A halogen is a strong inductive-withdrawing group *and* a weak resonance-donating group (the net effect is to be overall electron-withdrawing)

Note that, in the case of halogens, resonance effects are unusually weak and inductive effects are unusually strong, resulting in inductive effects outweighing resonance effects, a reversal of the usual trend. (Again, halogens are the exception to the rule!)

Critical Thinking Questions

59. Let us explore why halogens are deactivators, but *o/p* directors.



a. Halogens are powerful inductive-withdrawing groups. This means that a halogen **removes electron density from all six carbons of the ring**. Though the size of this effect is dependent on the distance from bromine, represent this at left by placing a LARGE $\delta+$ on each C of the ring.

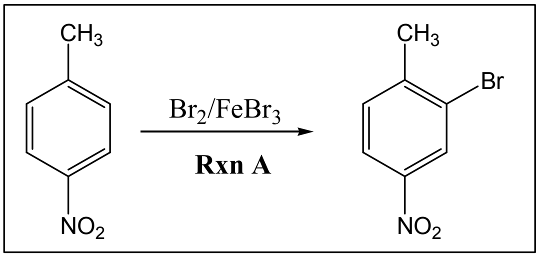
b. But, a halogen can resonance-donate back into the ring with one of its lone pairs (as demonstrated by second-order resonance structures).

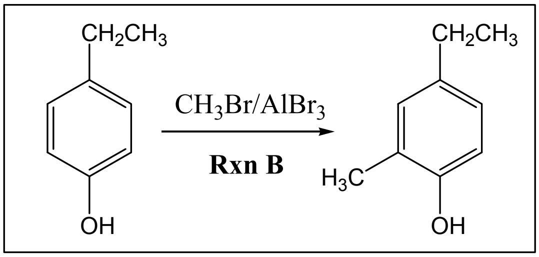
To represent this, on the structure of bromobenzene at left, put a small $\delta-$ next to the three ring carbons that receive electron donation from Br. (It may help to sketch 2nd order resonance structures of bromobenzene)

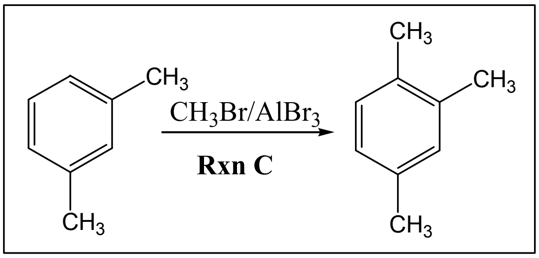
c. Circle the carbon**s** on bromobenzene that are most likely to bond to an electophile (E^+), and explain your reasoning.

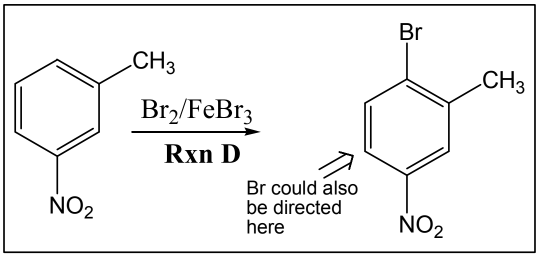
d. (Check your work) Is your answer to part c consistent with the fact that halogens are *o/p* directors?

Model 13: EAS Reactions with Di-Substituted Rings









Critical Thinking Questions

60. Consider the starting material in **Rxn A** in Model 13.
    a. (E) Mark the open position(s) on the ring where the CH_3 group would direct an E^+.
    b. (E) Mark the open position(s) on the ring where the NO_2 group would direct an E^+.
    c. (E) Are these two directing effects **opposed to one another** or **in agreement** (circle one)?

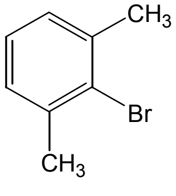
61. Consider the starting material in **Rxn B** in Model 13.
    a. (E) Mark the open position(s) on the ring where the ethyl group (Et) would direct an E^+.
    b. (E) Mark the open position(s) on the ring where the OH group would direct an E^+.

62. (Check your work) In **Rxn B** the directing effects of the two substituents are not in agreement.
    a. (E) According to the product in **Rxn B**, which substituent dominates (wins) in terms of directing effects, **the OH group** or **the alkyl (R) group**? (circle one)
    b. Based on the chart in Model 5 (found in Part B of this ChemActivity), which is a stronger activator, **an OH group** or **an alkyl (R) group**? (circle one)
    c. (Check your work) Are your answers to a and b of this CTQ consistent with one another?

Memorization Task 19.13: Two EAS activators in competition

When two EAS activators are in disagreement in terms of directing effects assume the stronger of the two activators "wins" and directs the placement of the electrophile.

63. Consider the starting material in **Rxn C** in Model 13.
    a. (E) Mark the open position(s) on the ring where each CH_3 group would direct an E^+.
    b. Construct an explanation for why the product below is formed in very small amounts compared to the product shown in **Rxn C**.



Minor Product

Memorization Task 19.14: Steric effects in EAS

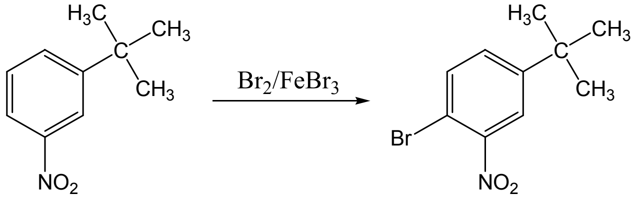
Placement of an electrophile between two groups is often unfavorable due to steric effects.

64. Consider the starting material in **Rxn D** in Model 13.
   a. (E) Mark the open position(s) on the ring where the CH_3 group would direct an E^+.
   b. (E) Mark the open position(s) on the ring where the NO_2 group would direct an E^+.
   c. According to the major product shown in **Rxn D**, which substituent dominates (wins) in a competition of directing effects between an activator and a deactivator?

Memorization Task 19.15: EAS activator in competition with an EAS deactivator

When an EAS activator is in disagreement in terms of directing effects with an EAS deactivator, assume the activator "wins" and directs the placement of the electrophile.

65. Consider an EAS starting material similar to the starting material in Rxn D, except with a *tert*-butyl alkyl group. This reaction yields the exclusive product shown below. Construct an explanation for why the Br group in Rxn D can be found either *ortho* or *para* to the methyl.



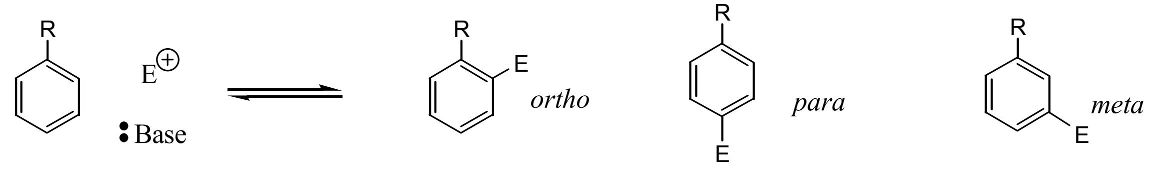
66. Consider Rxns A and D in Model 13, and construct an explanation for why replacing $Br_2/FeBr_3$ with $CH_3Br/AlBr_3$ leads to a much slower reaction, and a poor yield of corresponding alkylated products.

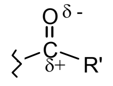
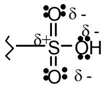
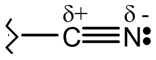
67. (Check your work) Is your answer to the previous question consistent with Memorization Task 19.3 (found in Part B of this ChemActivity)?

Memorization Task 19.16: Ring with two or more strong deactivators → very slow EAS

Only under extreme conditions will a ring with two or more strong **deactivators** undergo EAS.

Model 14: EAS Directing Effects (summary)

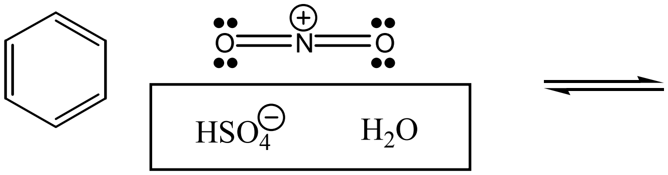


Identity of R	Inductive Effects	Resonance Effects	Product Regio-chemistry	Relative Reaction Rate
Anilines $-\ddot{N}H_2$, $-\ddot{N}HR$, $-\ddot{N}R_2$	weak e^- **withdraw**	strong e^- **donation**	*ortho & para*	very very fast
Phenols $-\ddot{\underset{\cdot\cdot}{O}}H$, $-\ddot{\underset{\cdot\cdot}{O}}R$	moderate e^- **withdraw**	strong e^- **donation**	*ortho & para*	very fast
Alkyl groups $-CH_3$, $-CH_2CH_3$ etc.	weak e^- **donation***		*ortho & para*	medium fast
Benzene $-H$	—	—	—	1
Halogens $-\ddot{\underset{\cdot\cdot}{I}}:$ $-\ddot{\underset{\cdot\cdot}{Br}}:$ $-\ddot{\underset{\cdot\cdot}{Cl}}:$ $-\ddot{\underset{\cdot\cdot}{F}}:$	strong e^- **withdraw**	weak e^- **donation**	*ortho & para*	slow
Acyl groups 	strong e^- **withdraw**	strong e^- **withdraw**	*meta*	very slow
Sulfate group 	strong e^- **withdraw**	strong e^- **withdraw**	*meta*	very slow
Nitro group $-NO_2$	strong e^- **withdraw**	strong e^- **withdraw**	*meta*	very slow
Cyanide group  $-\overset{\delta+}{C}\equiv\overset{\delta-}{N}:$	strong e^- **withdraw**	strong e^- **withdraw**	*meta*	very slow
Ammonium $-\overset{\oplus}{N}R_3$ (R = alkyl or H)	Very strong e^- **withdraw**	—	*meta*	very slow

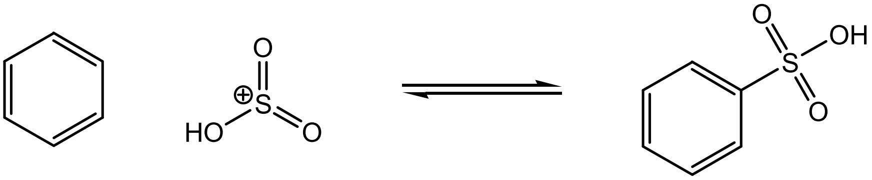
**Electron donation by an alkyl group can be considered an inductive or a pseudo-resonance effect (See hyperconjugation). Hyperconjugation cannot be demonstrated with second-order resonance structures.*

Exercises for Part A

1. Show the mechanism and most likely products that result from the following reactants. (Note: Two weak bases, water and bisulfate ion also are in solution.)



2. Sulfuric acid with absolutely no water in it is called **fuming sulfuric acid** and contains small amounts of the powerful electrophile $^+SO_3H$ (one resonance structure is shown below). Construct a mechanism for the following reaction.



3. Draw all possible resonance structures for the carbocation intermediate in Model 2.

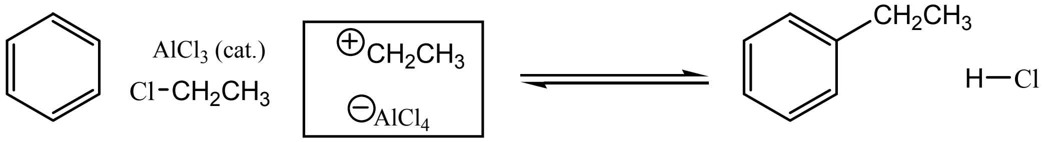
4. Violation of Memorization Task 19.1 with Synthetic Transformations 19.3 and 19.4 (e.g. use of $FeBr_3$ with Cl_2) gives rise to unwanted Br substitution products. Show the mechanism of formation of bromobenzene in an EAS reaction of benzene with $FeBr_3$ and Cl_2.

5. The rule in Memorization Task 19.1 is standard practice for Synthetic Transformations 19.5 and 19.6; however, violating it will not generate any unwanted side products. Explain.

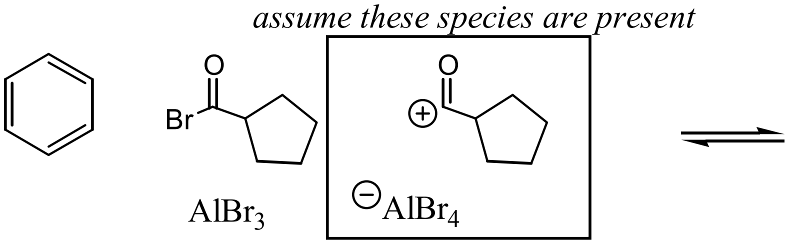
6. $^+NO_2$ is formed when nitric acid (HNO_3) and sulfuric acid (H_2SO_4) are mixed. Draw the Lewis structure of each and construct a mechanism that explains formation of $^+NO_2$. *Hint*: Water and HSO_4^- are the other products formed in this reaction.

7. When toluene is treated with sulfuric and nitric acids under special conditions, three nitro (NO_2) groups are substituted for hydrogens at the 2, 4 and 6 positions on the ring (the next section discusses why the 2, 4, and 6 positions are substituted). The product is a highly explosive substance called 2,4,6-trinitrotoluene. This substance is commonly known by a three letter name. What is it?

8. Construct a reasonable mechanism for the following reaction called a Friedel-Crafts alkylation. You may use curved arrows to show the formation of the carbocation electrophile in the box, or show the electrophile attached to the catalyst as in CTQ 12.

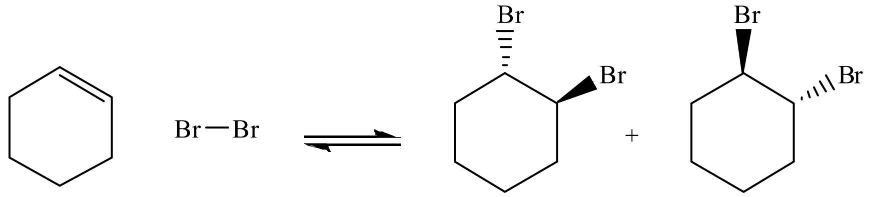


9. Draw the mechanism and most likely product(s) that result from the following EAS reaction called a Friedel-Crafts acylation. You may use curved arrows to show the formation of the carbocation electrophile in the box, or show the electrophile attached to the catalyst.

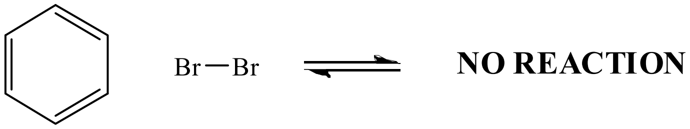


10. Consider the reactions below:

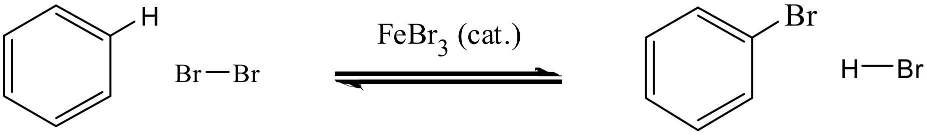
I.



II.



III.



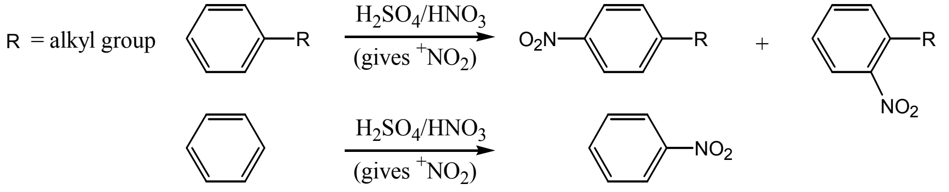
a. Why does Br_2 react with cyclohexene but not with benzene? (*See* Rxns I & II, above)

b. Construct a mechanism for Reaction III that shows $^{-}FeBr_4$ acting as a base in the last step, generating $FeBr_4H$, which decomposes into HBr and $FeBr_3$, regenerating the Lewis acid catalyst.

11. Read the assigned pages in your text and do the assigned problems.

Exercises for Part B

12. Recall that an alkyl group (R) is slightly electron-donating. This means it donates electron density into an attached aromatic ring. Based on this information, which of the following EAS reactions do you expect to be faster? Explain your reasoning.



13. Draw an example of an aromatic molecule that…

    a. will NOT undergo either Synthetic Transformation 19.5 or 19.6.

    b. *will* undergo Synthetic Transformations 19.5 or 19.6.

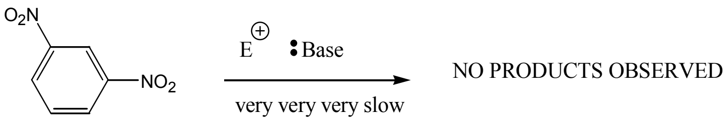
14. Of the choices in brackets, circle the word or phrase that makes the sentence true.

    a. The pi system of the ring acts as [**a nucleophile** *or* **an electrophile**] in an EAS reaction.

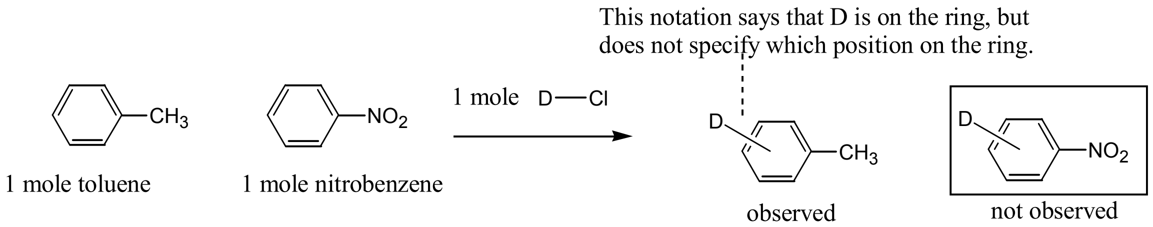
    b. The [**more** *or* **less**] electron-rich the pi system of the aromatic ring, the faster the rate of EAS.

15. A nitro group is a very powerful electron-withdrawing group. Which do you expect will undergo EAS reaction faster: **benzene** or **nitrobenzene** (circle one and explain your reasoning).

16. Construct an explanation for the following finding: Even with the best electrophile (E^+), di-nitro benzene undergoes EAS extremely slowly, so slowly that only trace amounts of product are observed under normal conditions.



17. When a flask containing a mixture of one mole of nitrobenzene and one mole of toluene is treated with one mole of D-Cl, deuterium is incorporated into the toluene ring, but not the nitrobenzene ring. Explain. That is, why does the toluene "hog" all the D-Cl while the nitrobenzene does not get any?

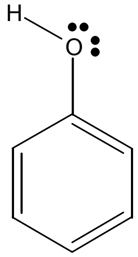

This notation says that D is on the ring, but does not specify which position on the ring.
CH_3
1 mole toluene
NO_2
1 mole nitrobenzene
1 mole D—Cl
D
CH_3
observed
D
NO_2
not observed

18. Read the assigned pages in your text and do the assigned problems.

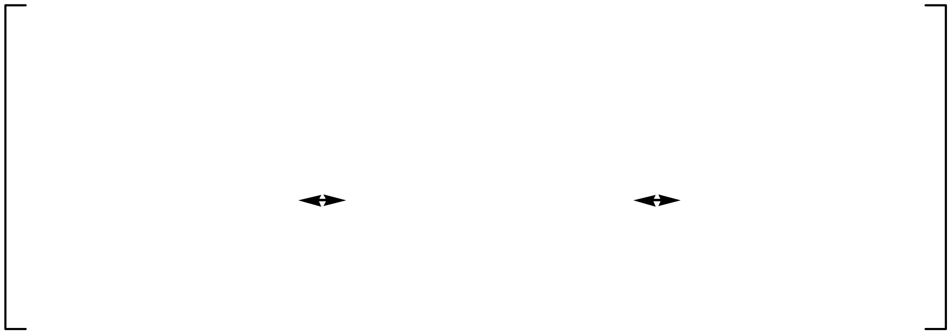
Exercises for Part C

19. Draw as many different constitutional isomers as you can of a mono-substituted benzene ring in which the single subsituent has a molecular formula C_2H_4NO and includes a carbonyl group (C=O). [There are 8 possibilities, of which 3 are resonance electron-donating groups, and 2 are resonance electron-withdrawing groups.]
    a. Label the isomers that are resonance electron-donating groups.
    b. Label the isomers that are resonance electron-withdrawing groups.
    c. For each, identify whether the isomer's substituent is a strong *o/p* director, strong *m* director, weak *o/p* director, or weak *m* director.

20. Draw three second-order resonance structures for phenol.



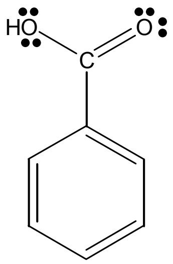
phenol



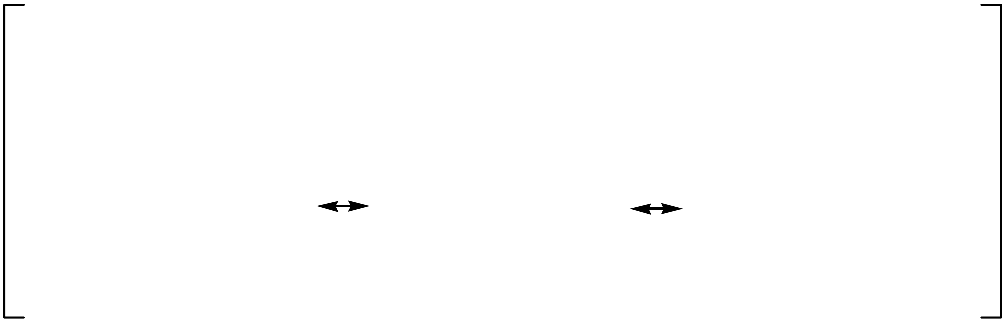
a. Explain why the second-order resonance contributors are less important than first-order resonance structures, and contribute only a small amount to our overall understanding of phenol.

b. Explain the following statement: The second-order resonance structures help explain why substituents with a lone pair (such as –OH) activate the *ortho* and *para* positions toward electrophilic aromatic substitution (EAS).

21. Draw three second-order resonance structures for benzoic acid.



benzoic acid

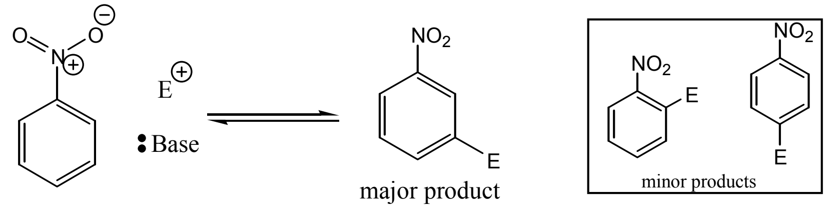


a. Based on these second-order resonance structures, do you expect the carboxylic acid group (COOH) to be a resonance-donating group or a resonance-withdrawing group?

b. Explain the following statement: The second-order resonance structures help explain why a carboxylic acid group **deactivates** the *ortho* and *para* positions toward electrophilic aromatic substitution (EAS).

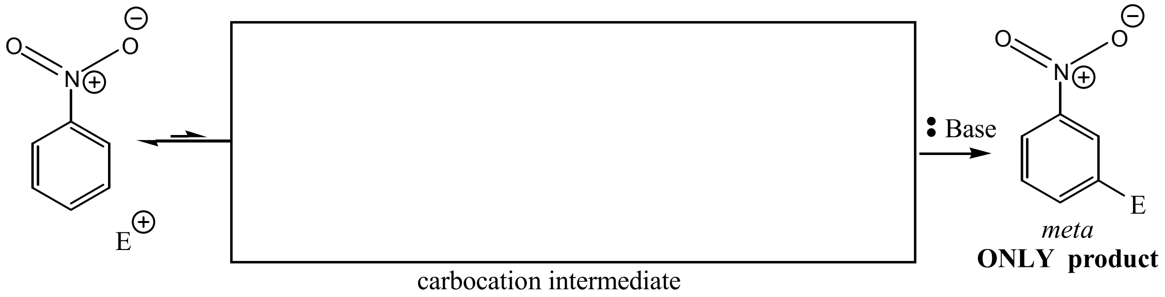
22. We have found that second-order resonance structures can be used to predict the regiochemistry of an EAS reaction. A more rigorous prediction comes from the heights of the activation barriers. According to the Hammond Postulate, the relative energies of the intermediates can be used to approximate the relative heights of these activation barriers. Simply put… **The pathway with the most favorable carbocation intermediate will likely dominate the product mixture.**

Consider electrophilic aromatic substitution (EAS) performed on nitrobenzene.

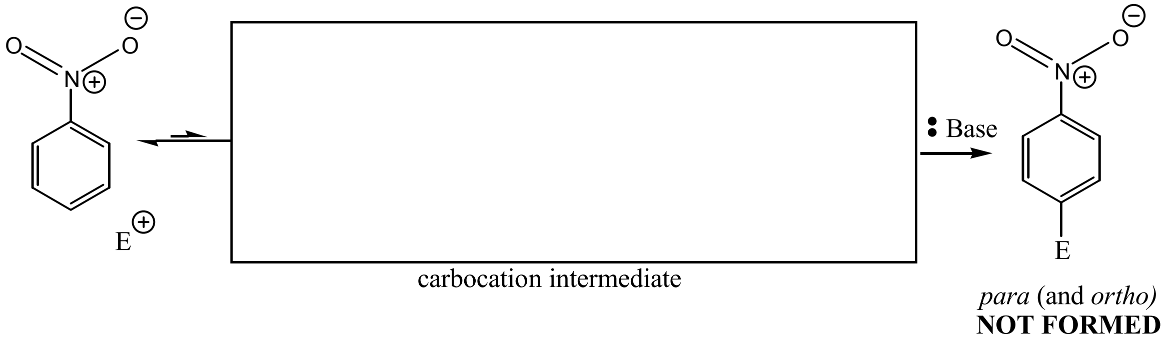


a. How does the placement of E^+ on the nitrobenzene ring differ from an EAS reaction starting with toluene or aminobenzene (aniline)?

b. Draw the intermediate on the reaction pathway to the major (*meta*) product. (Be sure to include **all important resonance structures**.)



c. Draw the intermediate on the reaction pathway to the *para* product. (Be sure to include **all important resonance structures**.)



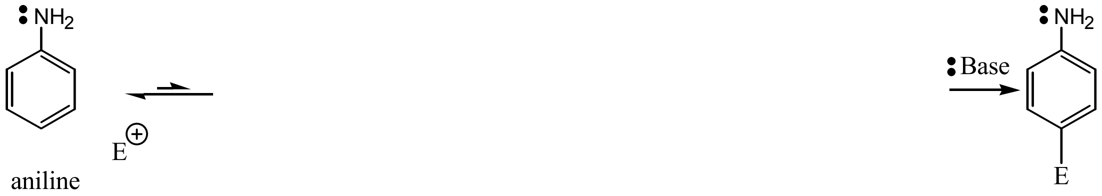
d. Any resonance structure in which two + charges are next to each other is very unfavorable. Circle all unfavorable resonance structures above.

e. Construct an explanation for why the intermediate on the reaction pathway to the *meta* product is lowest in potential energy.

f. Draw an energy diagram showing all three pathways (*ortho, meta* and *para)*.

g. Construct an explanation for why the *meta* product is strongly favored in this reaction over the *para* (and *ortho*) product.

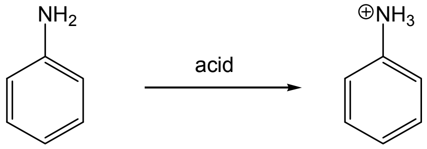
23. Aniline gives only *ortho* and *para* products in an EAS reaction.
    a. Draw the intermediate on the reaction pathway to the *para* product. Be sure to draw all **FOUR** important resonance structures.



    b. Draw the intermediate on the pathway to the *meta* product.
    c. Construct an explanation for why the intermediate on the pathway to the *meta* product is higher in potential energy than the intermediate on the pathway to the *para* product.
    d. Draw an energy diagram showing all three pathways (*ortho, meta* and *para).*

24. Aniline reacts with a given electrophile 100 times faster than toluene and 1000 times faster than benzene.
    a. Explain why an EAS intermediate for aniline such as the one in part a above is lower in potential energy than the intermediate you drew for *para*-substitution of toluene.
    b. Construct an explanation for why aniline undergoes EAS much faster than toluene.

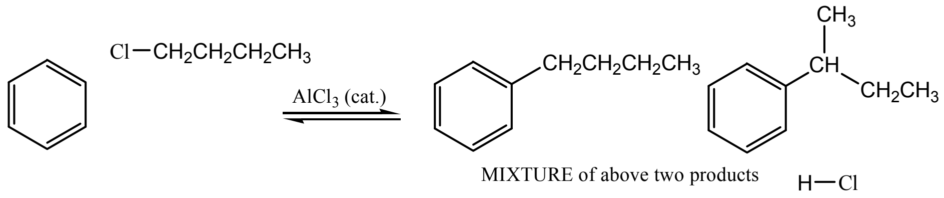
25. If you add acid to aniline you change the amine group (NH_2) into an ammonium ion group ($^{+}NH_3$). Draw the intermediate carbocations on the pathways to the *meta* and *para* products, respectively; predict whether an ammonium ion group is an *o/p* director or a *m* director; and explain your reasoning.



26. Read the assigned pages in your text and do the assigned problems.

Exercises for Part D

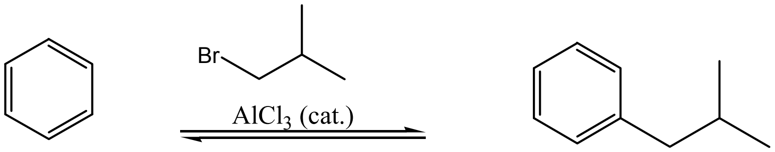
27. Draw a mechanism to explain the formation of each of the two Friedel-Crafts products. *Hint*: Think of (and draw) the $R^{\delta+}$ group in the R–X–$AlCl_3$ complex as a carbocation (R^+), then think about possible carbocation rearrangements.



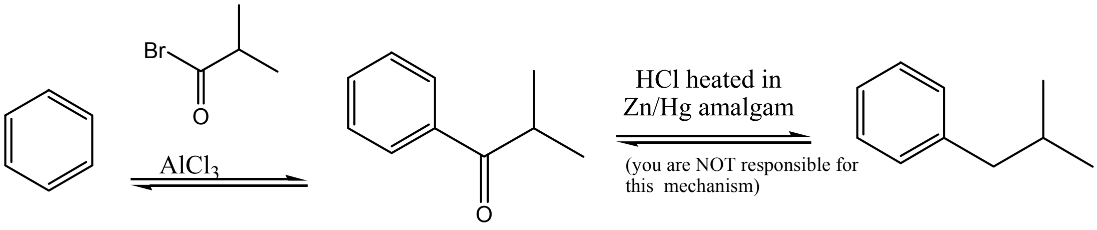
28. Give an example (not appearing in this ChemActivity) of an alkyl halide (R–X) that will
    a. likely undergo rearrangement during a Friedel-Crafts alkylation.
    b. NOT undergo rearrangement during a Friedel-Crafts alkylation.

29. Shown below are two ways of making the same target product starting from benzene. Synthetic pathway b gives a higher % yield of the desired product. Explain why.

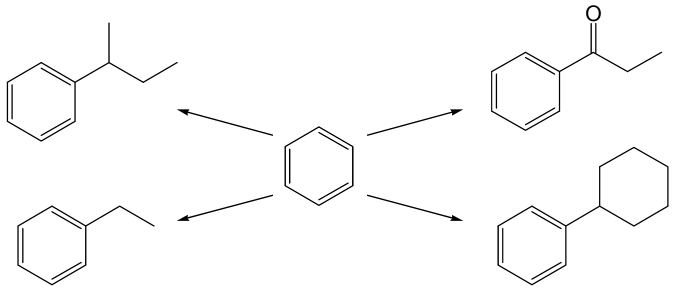
a



b



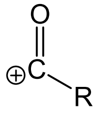
30. What reagents could you use to carry out the following reactions?



31. If you mix one mole of benzene + one mole of sulfuric acid + one mole of nitric acid you will isolate only one of the products shown in **Reaction Sequence I** (Model 9). What is this single product? Explain why only this product is formed.

32. Explain why Reaction Sequence II in Model 9 yields a large amount of unreacted benzene starting material when equimolar portions of benzene and electrophile are mixed.

33. Draw all important resonance structures for the following carbocation. This resonance stabilization is used to explain that acyl carbocations do not rearrange like alkyl carbocations.

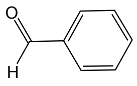


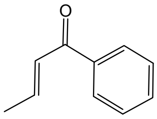
34. For CTQ 52, draw the F-C mono-alkylation product that is formed in each reaction if the electrophile reacts before a rearrangement can occur.

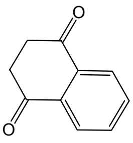
35. CTQ 52 implies that using a huge excess of benzene will reduce the likelihood that polyalkylation products will form. Construct an explanation for why this works.

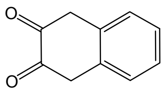
36. What special conditions allow reduction of the π bonds in an aromatic ring?

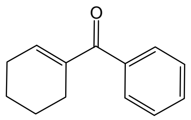
37. Predict the major product if each of the following molecules are treated with excess Zn(Hg)/HCl. Then draw the products that result if they are treated with excess H_2 and palladium.

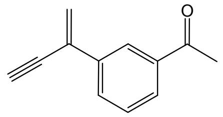




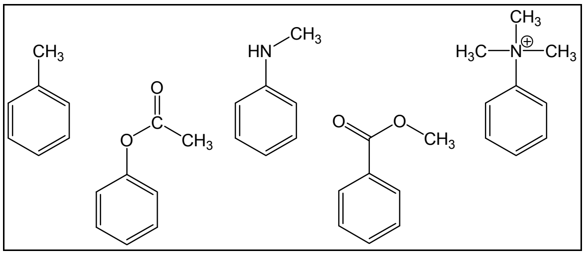


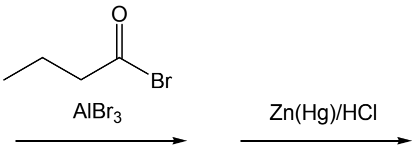




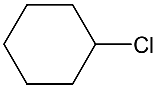


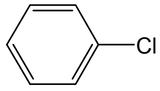
38. Predict the major product (if any) when each starting material is treated with these reagents, and specify how many molar equivalents of catalyst are necessary to maximize this product. *Note*: If the amount of catalyst is not specified, assume an appropriate amount is used to maximize yield.

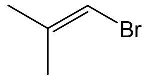


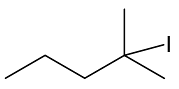


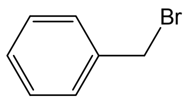
39. Draw the mono-substitution product (if any) that results when toluene is treated with $AlCl_3$ and each of the following halides (assume a large excess of toluene).







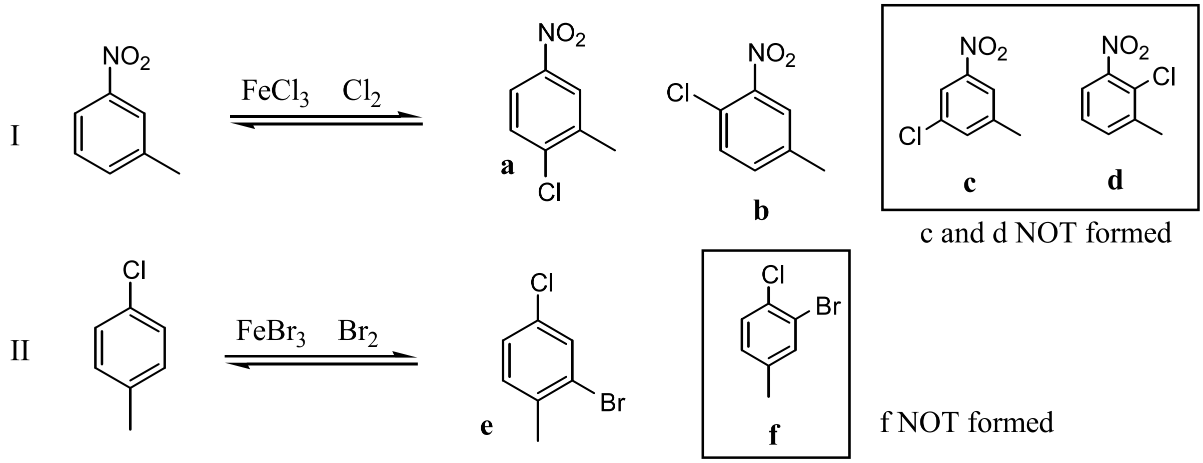




40. Read the assigned pages in your text and do the assigned problems.

Exercises for Part E

41. Consider the following reactions:



c and d NOT formed

f NOT formed

a. Construct an explanation for why Product **c** is not formed in Rxn I.

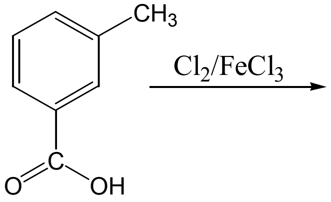
b. Construct an explanation for why Product **d** is not formed in Rxn I.

c. Construct an explanation for why Product **f** is not formed in Rxn II.

42. In the reaction below, two major products are observed.

a. Draw them, and construct an explanation for why they are formed instead of the other two possibilities.

b. Which of the two major products do you expect to dominate and why?



43. Mark each of the following statements True or False based on your current understanding. (**If false**, cite an example of a substituent for which it is false.)

a. T or F: A strong activator overpowers the directing effects of a weak activator.

b. T or F: A weak activator overpowers the directing effects of a deactivator.

c. T or F: All activators are *o/p* directors.

d. T or F: All deactivators are *m* directors.

44. Circle each of the following that helps explain why EAS with fluorobenzene is slower than EAS with phenol (hydroxybenzene)?

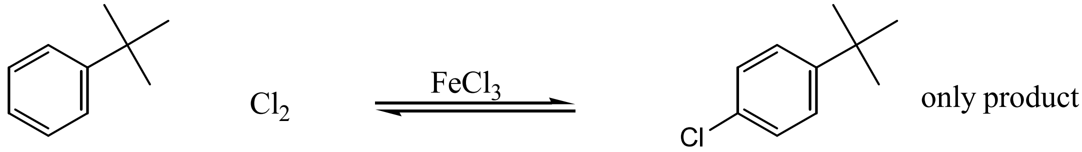
    (1) F is more electronegative than O, generating stronger inductive effects.

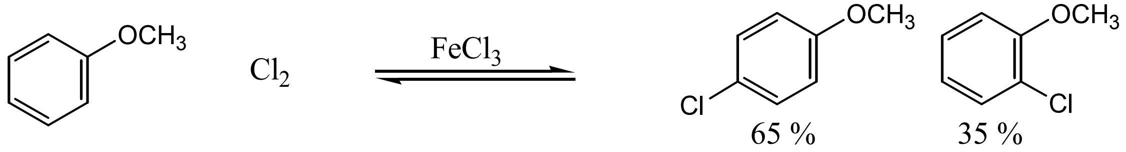
    (2) F holds it lone pairs very tightly, making it a weaker pi donator than O.

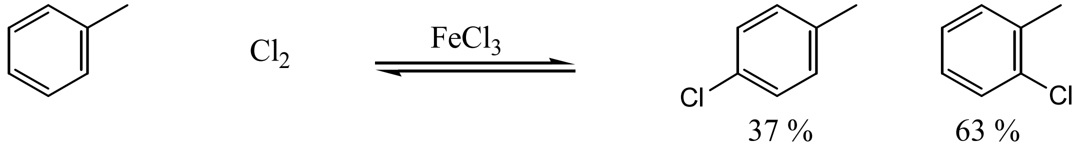
    (3) F has more lone pairs than O.

    (4) F is smaller in size than O.

45. Consider the following reactions:

I


II


III


a. Construct an explanation for why only the *para* product is observed in reaction I.

b. Fact: Neglecting steric effects, the expected ratio of *para:ortho* is 1:2 for reactions I, II and III. Why is Reaction III closest to the expected 1:2 ratio?

46. Read the assigned pages in your text and do the assigned problems.

The Big Picture

EAS tends to be a fairly straightforward unit. The key is memorizing all the many restrictions, especially those revolving around the Friedel-Crafts reactions. These reactions are one of only a handful of ways you will learn to make carbon-carbon bonds in this course, and the reactions are very commonly used for this purpose in the laboratory.

This ChemActivity did not stress synthesis, but it is coming. The next ChemActivity covers a reaction that is in many ways complementary and opposite to EAS. It is called NAS (Nucelophilic Aromatic Substitution). As the name implies, in NAS the aromatic ring functions as a nucleophile instead of an electrophile. During the next ChemActivity a primary goal should be to distinguish EAS from NAS. It can get quite confusing.

The ChemActivity after NAS (Synthesis Workshop 2) will try to bring the two together and showcase general strategies for synthesizing aromatic targets using EAS, NAS, and side chain reactions, often starting from benzene.

Common Points of Confusion

- Students get confused and assume that because a nitro group is a *meta* director, it must therefore add *meta* to whatever group is already on the ring. This is not the case. The preferred substitution position of the nitro group (or any other electrophile added in an EAS reaction) depends on whether the group ALREADY ON THE RING is an *o/p* or *m* director. For example, in Model 6, treatment of toluene with nitric and sulfuric acids yields almost exclusively *ortho*- and *para*-nitrotoluene because the alkyl group on the starting material is an *o/p* director. Whether the group being added (nitro in this case) is a *m* director or *o/p* director is irrelevant to placement of the electrophile in an EAS reaction.
- Students often confuse Friedel-Crafts reagents for EAS halogenation reagents. This happens especially often with the reagents CH_3Br and CH_3Cl. These reagents do NOT DELIVER A BROMINE/CHLORINE ATOM; they deliver a methyl group. Br_2 or Cl_2 (not an alkyl halide!) is used (in conjunction with an appropriate Lewis acid catalyst) to replace an H with a halogen on an aromatic ring.
- Friedel-Crafts reactions do not work when a strong electron-withdrawing group is present. Because the catalysts for F-C reactions are similar to the catalysts for halogenation EAS reactions (AlX_3 vs. FeX_3), students sometimes assume that none of these reactions work with deactivated rings. However, halogenation EAS reactions can still work with deactivated rings.
- No ordinary EAS reactions work with very deactivated rings. As a rule of thumb, a ring is considered very deactivated if it has two resonance electron-withdrawing groups (and no resonance electron-donating groups to counterbalance this).
- Students often notice that the presence of a carbonyl group on a substituents means that it is a *meta* director. Be careful with this. The group is a *meta* director only if the carbonyl is directly adjacent to the aromatic ring. See Exercise 38 for an example of a *meta* director and an isomeric molecule that is an *o/p* director.

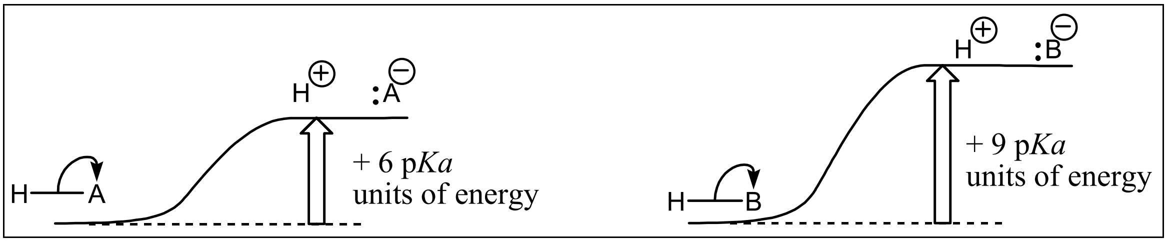
ChemActivity 20: Acidity and pK_a of Phenols

(How does the position of an electron withdrawing or donating group affect pK_a?)

Model 1: Review of pK_a

Consider the hypothetical acids H–A and H–B…

	Acid	pK_a	Conjugate Base	pH when [HX] = [X$^-$]	Energy Required to Break H–Z Bond
Acid No. 1	H–A	6	A$^-$	6	6 p*Ka* units of energy
Acid No. 2	H–B	9	B$^-$	9	9 p*Ka* units of energy



Acid-base reactions are very fast and usually come to equilibrium within seconds.

Critical Thinking Questions

1. According to the pK_a data, which is a stronger acid, **HA** or **HB** (circle one)?

2. According to Model 1, which acid requires **more** energy to remove the H$^+$? (Is this consistent with your answer to CTQ 1?)

3. A **buffer** (by a mechanism we will not discuss here) can be used to "set" the **pH** of a solution and keep it there. In practice you can buffer a solution to almost any pH between two and 12.
   a. To what pH would you "set" your solution of HA in water if you want [HA] = [A$^-$] (the concentration of HA = the concentration of A$^-$)?

Memorization Task 20.1: Relationship of pH to [H$^+$] and [HO$^-$]

- **Raising the pH** of a solution **raises the [HO$^-$]** and lowers the [H$^+$] in solution.
- **Lowering the pH** of a solution **raises the [H$^+$]** and lowers the [HO$^-$] in solution.

Recall that for all solutions $[H^+]$ x $[HO^-]$ *= a constant =* 10^{-14}

   b. Assume you raise the pH of your HA solution to pH 7 from pH 6. Which is greater when the solution comes to equilibrium at pH 7, **[HA]** or **[A$^-$]**? Explain your reasoning.

Memorization Task 20.2: Changing pH by one changes $[HA]:[A^-]$ ratio by factor of 10.

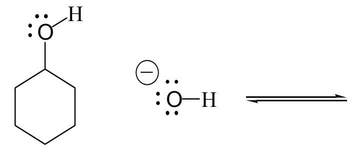
For example: At **pH** 6 the hypothetical acid HA (*See* Model 1.) has an $[HA]:[A^-]$ ratio of 1:1.
At pH 7 the $[HA]:[A^-]$ ratio is 1:10, and at pH 8 the $[HA]:[A^-]$ ratio is 1:100, etc.

4. Complete the following tables of [conjugate acid]:[conjugate base] ratios for HA and HB.

Acid HA (pK_a 6)	
pH	**$[HA]:[A^-]$**
4	
5	
6	1:1
7	1:10
8	1:100
9	
10	
11	

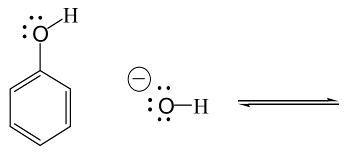
Acid HB (pK_a 9)	
pH	**$[HB]:[B^-]$**
4	
5	
6	
7	
8	
9	
10	
11	

Model 2: Acidity of Cyclohexanol vs. Phenol



cyclohexanol

conjugate base of cyclohexanol (w/ resonance structures–if any)



phenol

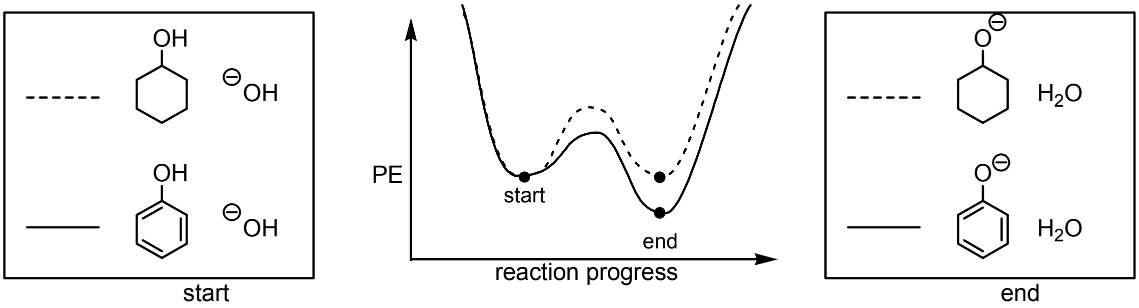
conjugate base of phenol (w/ resonance structures–if any)
"**phenoxide ion**"

Critical Thinking Questions

5. Show the most likely **acid-base reaction** between each pair of reactants in Model 2, and draw the conjugate base that results, **including all important resonance structures** (if any).

6. Which conjugate base do you expect to be **lower in potential energy**? Explain your reasoning.

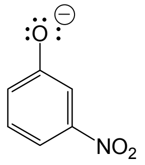
7. Construct an explanation for why the reaction of hydroxide with cyclohexanol is approximately thermoneutral while the reaction of hydroxide with phenol is down hill (exothermic).



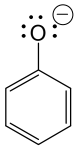
8. Which alcohol (**cyclohexanol** or **phenol**) is more acidic? (circle one)

9. (Check your work.) The pK_a of phenol is 10. The pK_a of cyclohexanol is 17. Is this consistent with your conclusions above?

10. A nitro group (abbreviated NO_2) is an electron-withdrawing group. Circle the ion you expect to be lower in potential energy, and explain your reasoning.



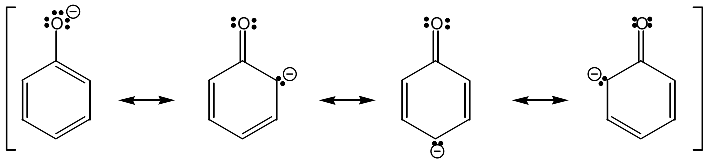
meta-nitrophenoxide ion
(one of several resonance structures)



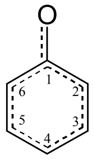
phenoxide ion
(one of several resonance structures)

11. Predict which acid has a lower pH (is more acidic), ***meta*-nitrophenol** or **phenol**. (circle one)

12. Use curved arrows to show generation of the set of resonance structures at right for phenoxide.



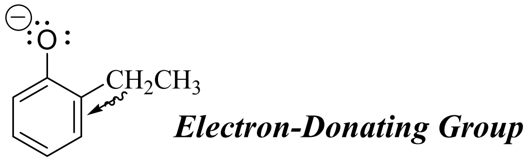
13. Based on the resonance description of phenoxide ion on the previous page, complete the composite structure of phenoxide ion (at right) by placing δ– where appropriate.



14. At which positions on the phenyl ring do you expect an **electron-withdrawing group** to have the greatest impact on lowering the potential energy of the phenoxide ion?

2*(ortho)* 3*(meta)* 4*(para)* 5*(meta)* 6*(ortho)* (circle all that apply)

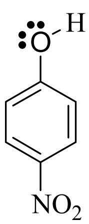
15. Do you expect an **electron-donating group** (such as an alkyl group) to stabilize (lower the P.E. of) or destabilize (raise the P.E. of) a phenoxide ion? Explain your reasoning.

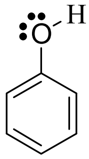


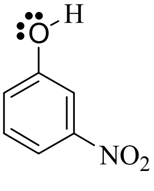
16. At what position(s) on the ring would you expect such an electron-donating group to have the greatest impact at raising the potential energy of the phenoxide ion?

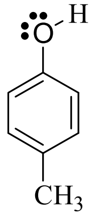
2*(ortho)* 3*(meta)* 4*(para)* 5*(meta)* 6*(ortho)* (circle all that apply)

17. Number the following phenols **from most acidic to least acidic,** and explain your reasoning. (1 = most acidic…4 = least acidic).

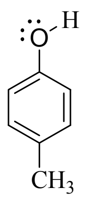


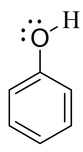


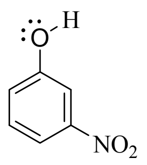


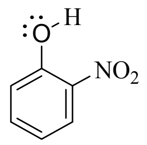


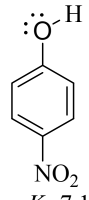
Model 3: pK_a Values for Various Substituted Phenols

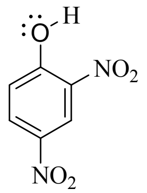

pK_a 10.26

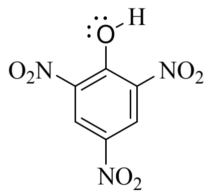

pK_a 10


pK_a 8.4


pK_a 7.22


pK_a 7.15


pK_a 4.09


pK_a 0.25

Critical Thinking Questions

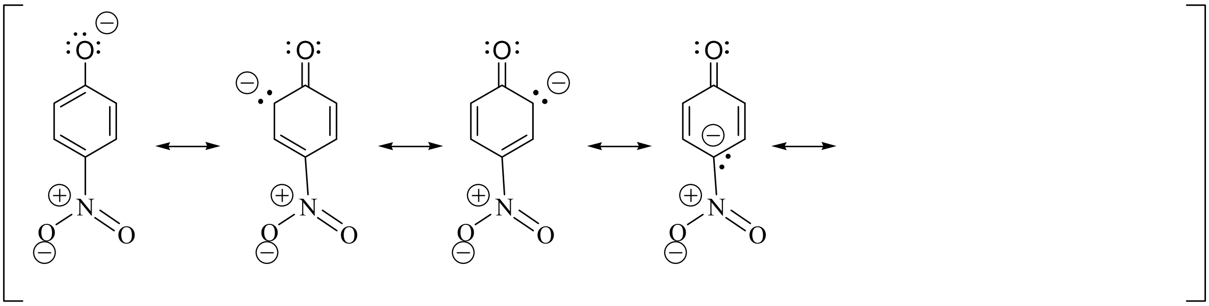
18. (Check your work.) Are your predictions in the previous question consistent with the data above?

19. Below the tri-nitro phenol, draw its conjugate base.

    a. Is this conjugate base the highest P.E. or the lowest P.E. among the conjugate bases of structures in Model 3?

    b. Explain your reasoning.

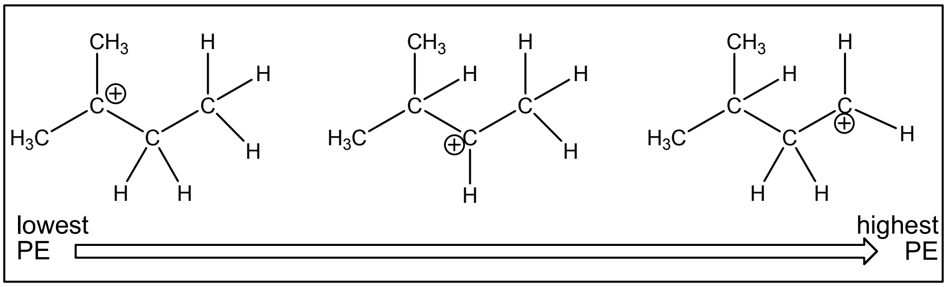
20. Below are four resonance structures of the conjugate base of *para*-nitrophenol with the nitro group drawn as a full Lewis structure. Draw a fifth resonance structure that shows that nitro **withdraws electrons from the ring via resonance effects.**



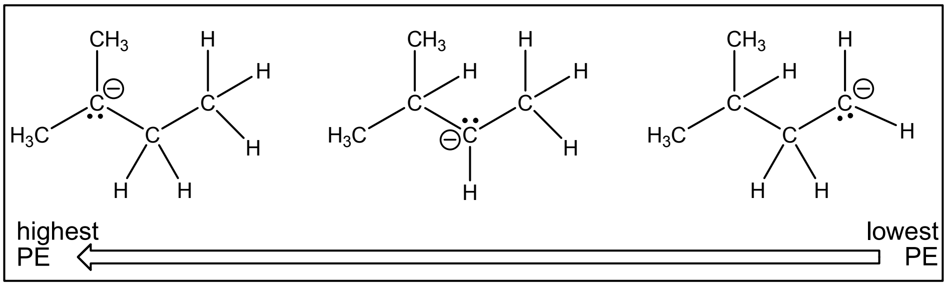
conjugate base of *para*-nitrophenoxide ion

Model 4: Carbanion (= Carbon with a negative charge)

Carbocations



Carbanions



Critical Thinking Questions

21. Label each **carbocation** and each **carbanion** in Model 4 as being primary (1°), secondary (2°), or tertiary (3°).

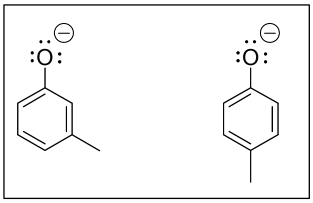
22. Complete the following statement: In terms of primary (1°), secondary (2°), or tertiary (3°), carbanions follow the **same** or **opposite** (circle one) trend as compared to carbocations.

23. Check your answer to the previous question against Mem. Task 20.3 at the end of the Exercises.

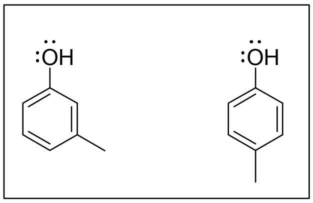
24. Are alkyl groups **electron-donating groups** or **electron-withdrawing groups** (circle one)?

25. Construct an explanation for why a tertiary carbanion is higher in P.E. than a primary carbanion?

26. Predict which conjugate base is higher in P.E. and, explain your reasoning.



conjugate bases



conjugate acids

27. The pK_a of *p*-methylphenol is 10.26. Predict if the pK_a of *m*-methylphenol is **higher** or **lower**, and explain your reasoning.

Exercises

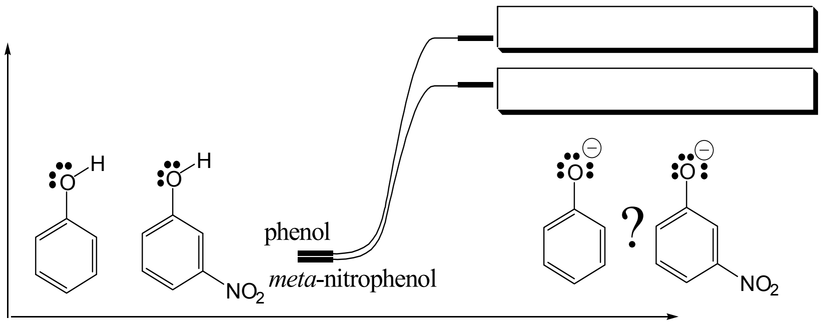
1. You put 1 mole of acid #2 (from Model 1) into an aqueous solution and exactly ½ of it (0.5 mole) dissociates into H_3O^+ and B^-, and the other half of it stays as H–B. What is the pH of this solution?

2. You put phenol in water buffered to pH 11. A minute later, which do you expect to be greater, **phenol** or **phenoxide ion** (circle one)?

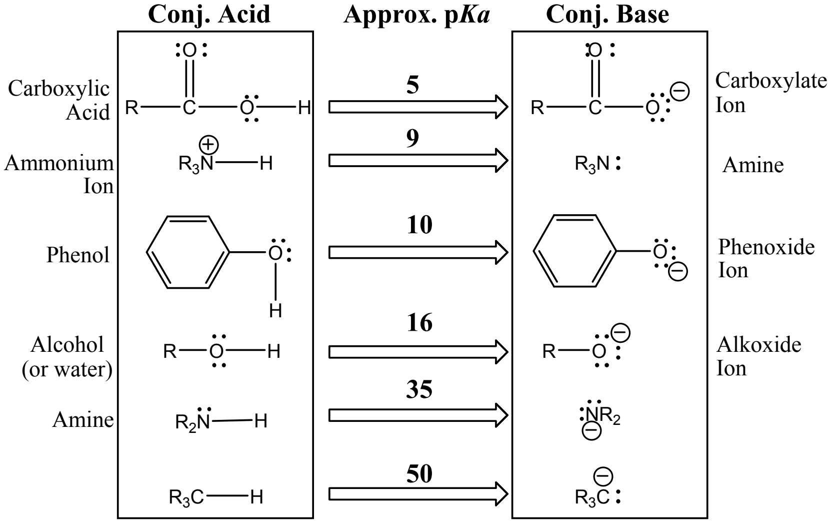
3. What is the following ratio at pH 14? $$\frac{[\text{phenoxide}]}{[\text{phenol}]} =$$

4. At what pH do you expect a buffered solution to be ≈99% phenol (and ≈1% phenoxide)?

5. Below is an energy diagram for removal of an H^+ from two different acids. Assume the two acids have about the same starting energy. Write the name ***meta*-nitrophenoxide ion** in one box, and **phenoxide ion** in the other box.



6. (Review) It is useful to memorize the following approximate p*Ka*'s:

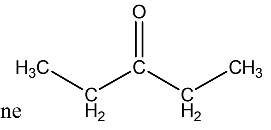


	Conj. Acid	**Approx. p*Ka***	**Conj. Base**	
Carboxylic Acid	$R-\overset{O}{\overset{\|}{C}}-O-H$	5	$R-\overset{O}{\overset{\|}{C}}-O^-$	Carboxylate Ion
Ammonium Ion	R_3N^+-H	9	$R_3N:$	Amine
Phenol		10		Phenoxide Ion
Alcohol (or water)	$R-O-H$	16	$R-O^-$	Alkoxide Ion
Amine	R_2N-H	35	$^-NR_2$	
	R_3C-H	50	R_3C^-	

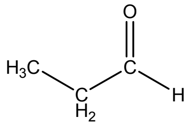
7. For the species in the table above, label the strongest base, strongest acid, weakest base and weakest acid.

8. What is the ratio of [carboxylic acid]/[carboxylate] in a solution buffered to pH 8?

9. Aldehydes and ketones have much lower pK_a values than you might expect given that removal of an H requires you to break a C—H bond. On each of the following compounds, identify the most acidic H (or H's if there is a tie), draw the conjugate base, and explain your reasoning.



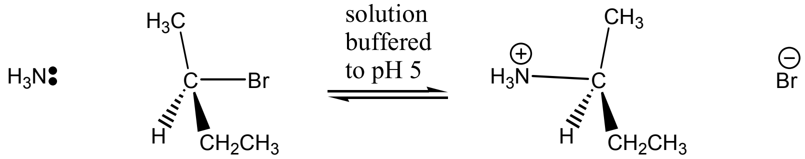
3-pentanone



propanal

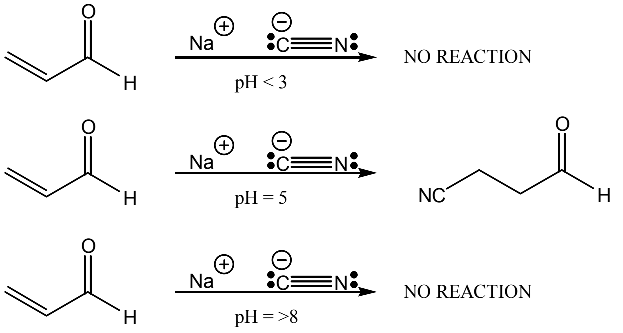
10. A typical aldehyde such as propanal has a pK_a of about 17, while a typical ketone such as 3-pentanone has a pK_a of about 19.
    a. According to the pK_a's which compound is more acidic?
    b. Construct an explanation for why this compound is more acidic. *Hint*: It is mostly due to electronic (not steric) factors.

11. It is recommended that the following nucleophilic substitution reaction be run with at least a 0.001 M (molar) concentration of ammonia (NH_3).

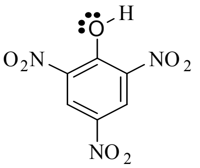
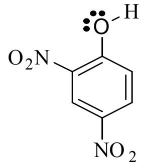
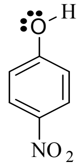
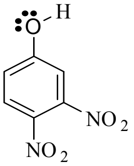
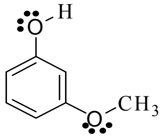
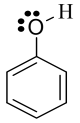
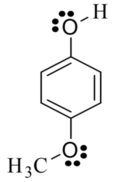
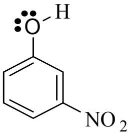


    a. Use curved arrows to show the mechanism of this reaction (Assume it is a one-step reaction.).
    b. What is the name of this type of reaction mechanism?
    c. Label the reactants and products with their absolute configuration (R or S).
    d. Because NH_3 is a toxic gas, you start by placing 1 mole of NH_4Br into a 1-L solution buffered to pH 5. At equilibrium, will the reaction be within the recommended NH_3 concentration?
    e. What is the minimum pH at which this reaction can be run?
    f. What is the problem with running the reaction below this pH?

12. Cyanide (also a toxic gas) has a pK_a of 9. For the transformation at right (which we will learn later), both H_3O^+ and cyanide ion (^{-}CN) are needed. Explain the results of each reaction arrow at right.



13. Number the following molecules from **least acidic** (**1**) to most acidic (8).

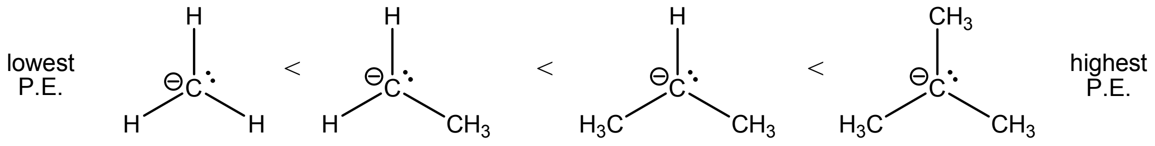









14. *Ortho* -nitrophenol is less acidic than *para*-nitrophenol. This is because an *ortho*-nitro group can form a hydrogen bond to the alcohol H.
    a. Draw the full Lewis structure of *ortho*-nitrophenol showing this hydrogen bond as a ---- (dotted line).
    b. Explain how this hydrogen bond increases the pK_a of *ortho*-nitrophenol relative to *para*-nitrophenol.

15. Draw all four resonance structures of the conjugate base of *para*-methylphenol. Circle the **least important (least favorable) resonance structure,** and explain your reasoning.

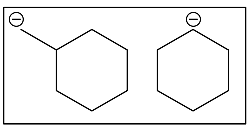
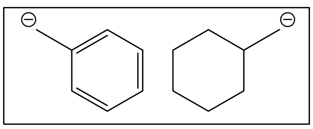
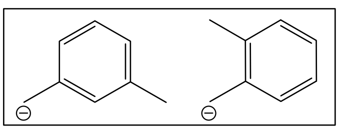
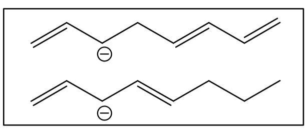
Memorization Task 20.3: Potential Energy Trends of Carbanions

Unlike carbocations, a **methyl carbanion** is lower in P.E. than a comparable **1° carbanion**, etc.



However, like carbocations, allylic and benzyllic carbanions are lower than ordinary carbanions due to resonance stabilization.

16. For each pair, circle the stronger base.

17. Draw all important resonance structures for each carbanion in the previous question that is resonance-stabilized.

18. Read the assigned pages in your text, and do the assigned problems.

The Big Picture

Much of this activity is devoted to review of acid/base chemistry, pK_a, and resonance stabilization. These are three of the most important concepts/skills required for this course. You would do well to take this opportunity to clear up any doubts or questions brought out by this activity or that linger unresolved from previous ChemActivities on these topics. To determine if you have such questions, go back and review ChemActivities 4 and 5. The better your understanding of these topics, the more likely you are to understand and enjoy the upcoming topics.

Acid/base chemistry, pK_a, and resonance stabilization are especially critical for understanding the next ChemActivity on Nucleophilic Aromatic Substitution (NAS).

This activity also serves as a break between EAS and NAS. These two topics have many similarities beyond their names, but in many critical ways they are opposite and complementary to each other. Before starting the next activity it would be wise to review EAS so that you do not get the two reactions confused.

Common Points of Confusion

Reread the Common Points of Confusion sections at the end of ChemActivities 4 and 5.

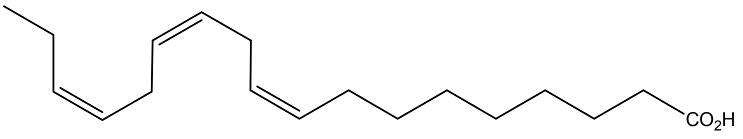
ChemActivity 21: NAS

(Why do some aryl halides undergo substitution reactions while others do not?)

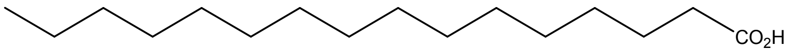
Model 1: Saturated and Unsaturated

The term **saturated** is used to describe an atom or molecule with the maximum number of σ bonds. For example, a carbon with four σ bonds is "**saturated** with σ bonds."

An **unsaturated** molecule (e.g., an unsaturated fatty acid) has one or more atoms that are not saturated with σ bonds. Almost always this means the molecule contains one or more π bonds.



Linoleic Acid
(an omega 6 fatty acid)



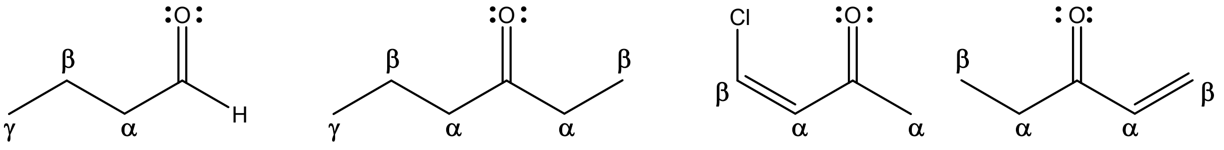
Palmitic Acid

Plants and animals do not make trans fatty acids (a fatty acid with one or more trans double bonds). Trans fats result from chemical alteration of natural fats, either on purpose (e.g., while making vegetable oil into margarine) or by accident (by leaving oil in a hot fryer for hours or days).

Critical Thinking Questions

1. (E) Which **fatty acid** above is saturated, and which is unsaturated?
2. (E) Circle each unsaturated carbon.
3. (E) Is the unsaturated fatty acid shown above a *trans* fatty acid? Explain your reasoning.

Model 2: *alpha* (α) and *beta* (β) Carbons of Carbonyl Compound



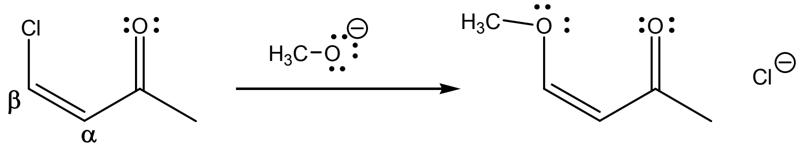
The Greek letter *alpha* (α) is used to label the carbon directly attached to a carbonyl group. The Greek letters *beta* (β), *gamma* (γ), etc., are used to label each successive carbon beyond that.

Critical Thinking Questions

4. (E) Both atoms of a carbonyl group (C=O) are **unsaturated**. Circle any other atoms in Model 2 that are **unsaturated**.

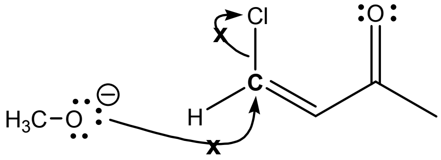
5. The two compounds on the right side of Model 2 are examples of **alpha,beta-unsaturated carbonyl compounds** (α,β-unsaturated carbonyl compounds). Explain this name.

Model 3: Substitution at the β-Carbon of an α,β-Unsaturated Carbonyl



Memorization Task 21.1: S_N1 and S_N2 reactions work only at *sp*³-hybridized carbons

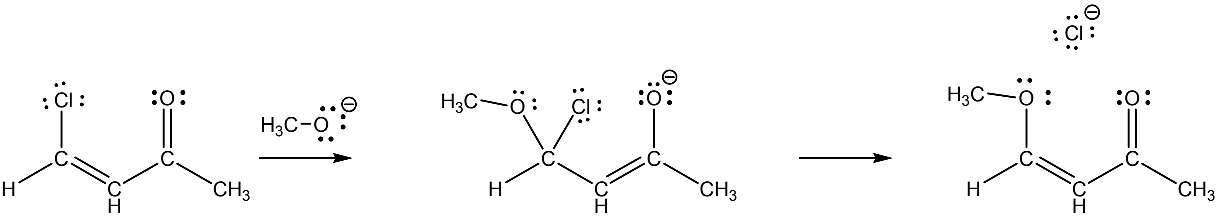
S_N2 and S_N1 work only with the leaving group on an *sp*³-hybridized carbon.



Critical Thinking Questions

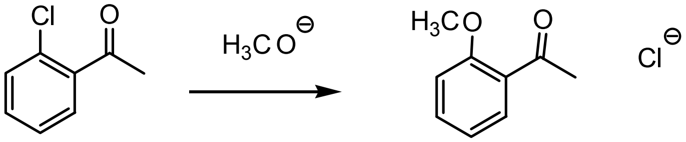
6. (E) What is the hybridization state of the carbon attached to Cl in Memorization Task 21.1?
7. (E) Explain why the curved arrows in Memorization Task 21.1 are crossed out.

8. Add curved arrows to complete the following two-step mechanism for the reaction in Model 3.



Model 4: Addition-Elimination on an Aromatic Ring

The reaction mechanism in the previous question is called **addition-elimination**. We will encounter several variations, but this activity focuses on its application to certain types of aromatic molecules.

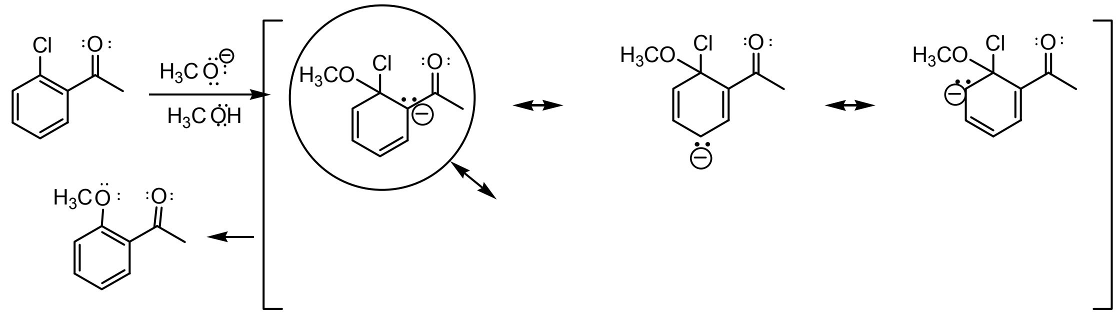


Critical Thinking Questions

9. Draw a mechanism for the reaction in Model 4.

10. Three resonance structures (r.s.) of the intermediate from the previous question are shown below.

Rxn I



a. Construct an explanation for why the circled r.s. is the most important of the ones shown.

b. Draw the fourth (and most important) resonance structure. (*Hint*: Start from the circled r.s.)

11. Which of the following true statements help explain why the resonance structure (r.s.) you drew above is the most important resonance structure in this set (circle all that apply):

(1) An anionic r.s. is more favorable if the negative charge is localized on O rather than C.

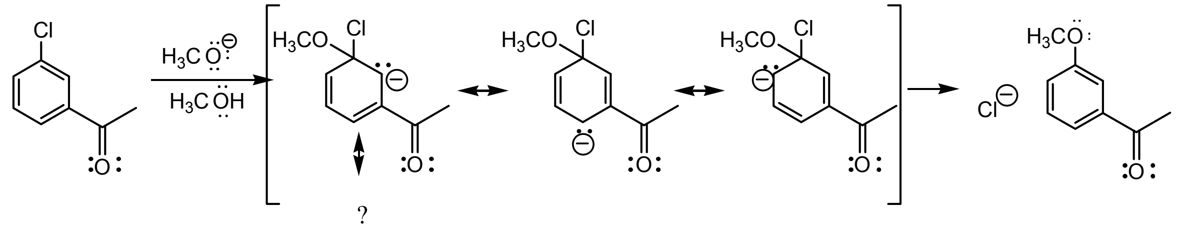
(2) A r.s. is more favorable if it is aromatic.

(3) A r.s. is more favorable if the negative charge is on a less-substituted carbon.

(4) A r.s. is more favorable if it has fewer overall formal charges.

12. Three resonance structures for the intermediate of Rxn II are shown below. Can you draw a fourth resonance structure that is aromatic and holds the negative charge on oxygen?

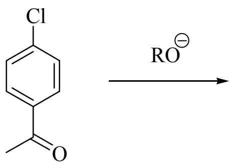
Rxn II



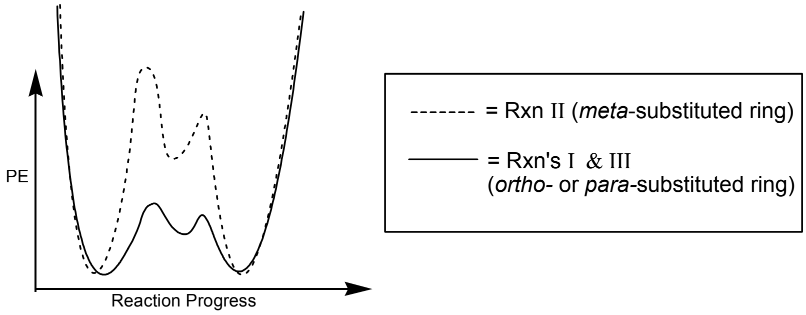
13. Are your answers above consistent with the fact that the *ortho*-substituted starting material yields significant product but the *meta*-substituted starting material does not?

14. Predict whether a *para*-substituted starting material such as the one on the right will yield significant product like *ortho* or not, like *meta*. (*Hint*: Draw the best r.s. of the intermediate.)

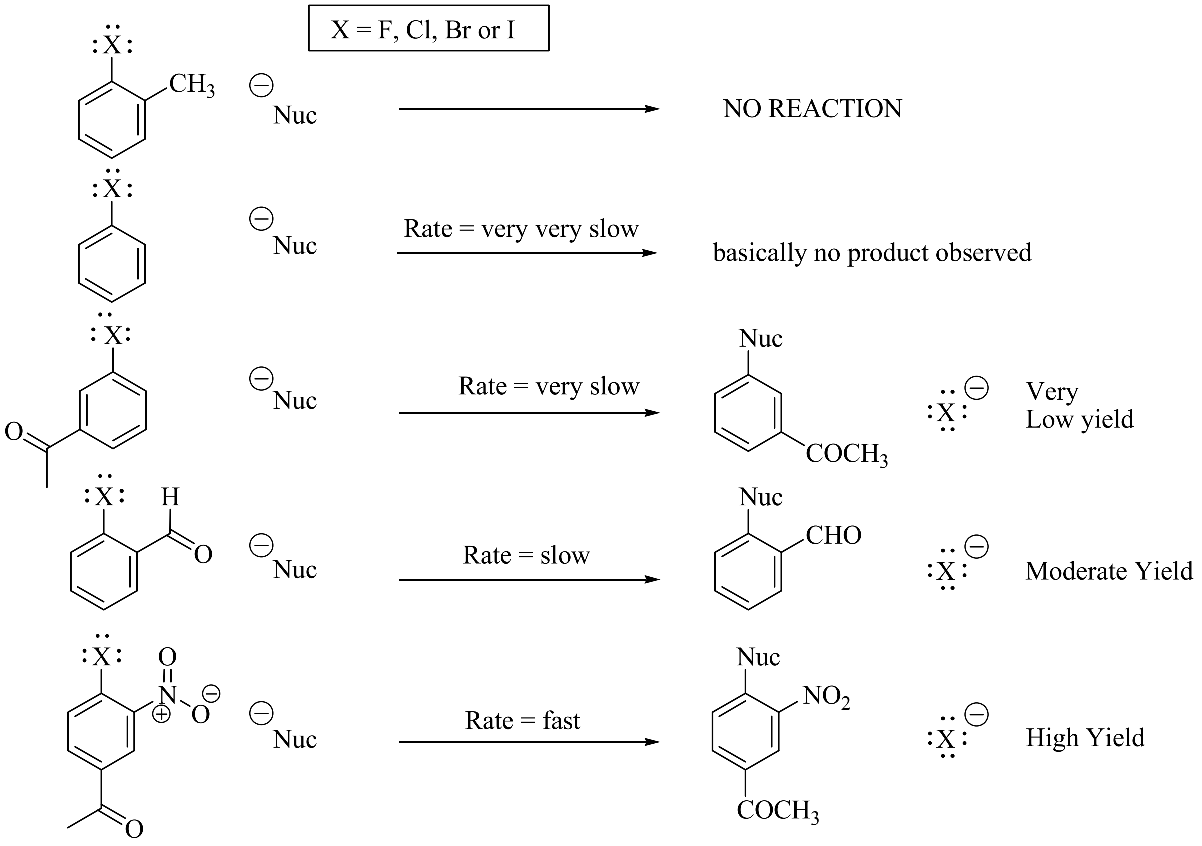
Rxn III



15. Is your conclusion in the previous CTQ consistent with the following energy diagram? Explain.



Model 5: Nucleophilic Aromatic Substitution (NAS)



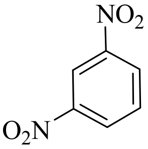
Critical Thinking Questions

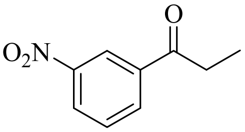
16. Circle the leaving group on each starting material in Model 5.

17. Put a box around each resonance electron-withdrawing group on the starting materials in Model 5.

18. Explain why NAS works well with one or more resonance electron-withdrawing groups *ortho* or *para* to the leaving group, but not when such a group is *meta*.

19. Construct an explanation for why neither of the aromatic rings at right will undergo NAS even though each has two resonance electron-withdrawing groups.



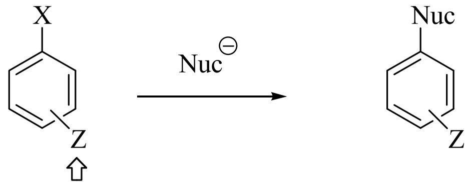


Memorization Task 21.2: For NAS to be favorable…

- There must be a leaving group on the aromatic ring (usually a halogen).
- You must use a very good nucleophile such as RO^{-} or R_3N (R = H or alkyl).
- There must be at least one strong **electron-withdrawing group (EWG)** *ortho* or *para* to the leaving group (usually a resonance EWG like nitro or a carbonyl).
- The more EWG's *ortho* and/or *para* to the leaving group the faster the rate of NAS.

Special NAS reactions can take place without electron-withdrawing groups on the ring. These require extreme conditions and likely go through what is called a ***benzyne intermediate*** *(explored further in the Exercises section of this ChemActivity).*

Synthetic Transformation 21.1: NAS (Nucelophilic Aromatic Substitution)



X = F, Cl, Br or I

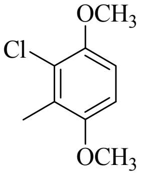
Z = Strong EWG, e.g. NO_2, carbonyl, or $\overset{\oplus}{N}R_3$

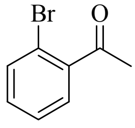
Nuc = $^{\ominus}OH$ $^{\ominus}OR$ or R_3N

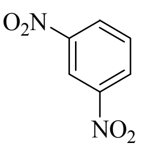
Under normal conditions there must be at least one EWG *ortho* or *para* to the leaving group. (Certain conditions do not require an EWG. See Synth. Transf's 21.2 and 21.3 in Exercises)

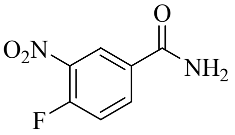
20. Match each term to a molecule to indicate whether it will undergo NAS, EAS, or neither.

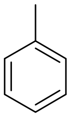
moderate NAS	**moderate EAS**	**neither** (*use twice*)
fast NAS	**fast EAS**	

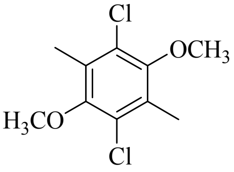












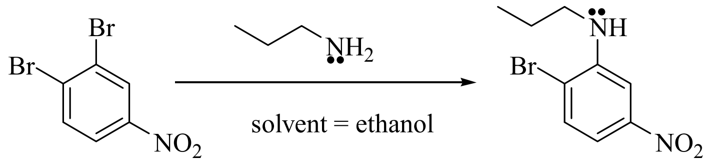
21. Make a list of key similarities and differences between NAS and EAS reactions.

Exercises

1. Explain the reasoning behind each answer in CTQ 20.

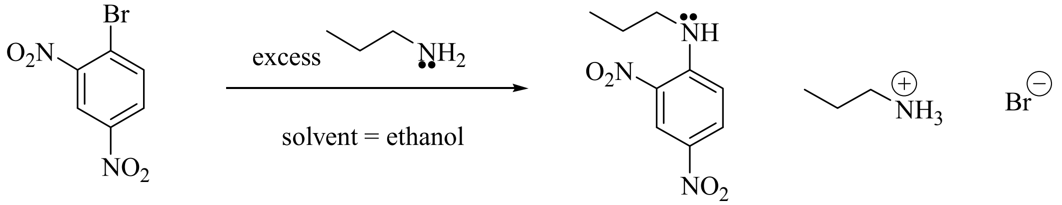
2. In an NAS reaction, is the aromatic ring acting as a **nucleophile** or as an **electrophile**? (How does this compare to an EAS reaction?)
   a. Based on your answer above, do you expect the reaction to be faster when the ring is substituted with **electron-withdrawing groups** or **electron-donating groups**? (Is your answer consistent with data in Model 5?)
   b. Draw a substituted aromatic ring that you expect will undergo NAS faster than any of the examples shown in Model 5.

3. The product shown does not form. Draw the correct product, and explain why it is formed instead of the one shown.



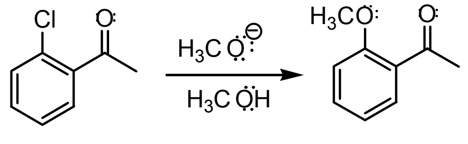
(This product DOES NOT FORM!)

4. Show a reasonable mechanism for the following reaction.

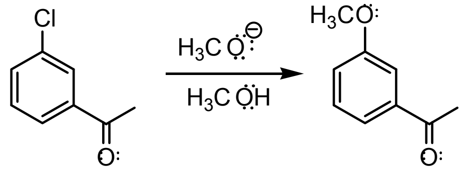


5. Consider the following NAS reactions (Only the first one yields significant product.):

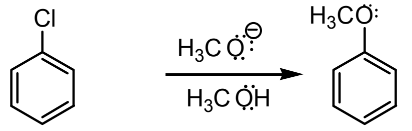
Rxn D

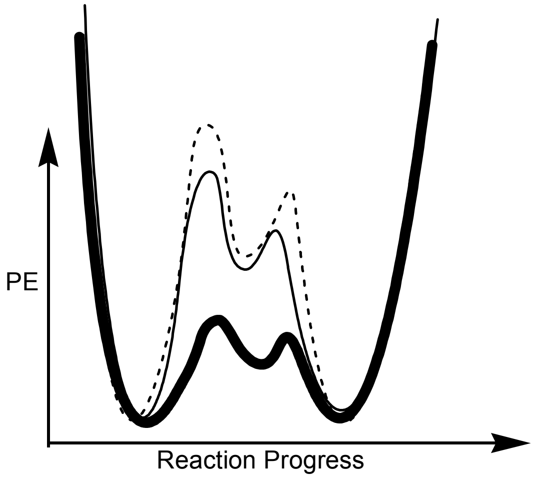


Rxn E



Rxn F





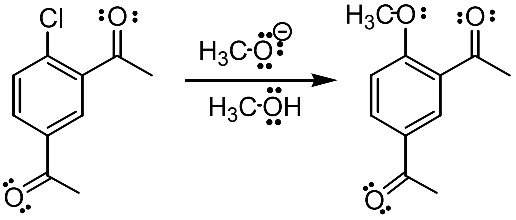
a. Draw the intermediate for each reaction including all important resonance structures.

b. Match each reaction to an energy-profile line on the energy diagram.

c. Construct an explanation for why the intermediate for Rxn E is slightly lower in P.E. than that of Rxn F (even though both reactions are very slow and yield almost no products).

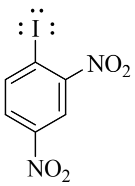
d. Draw all five resonance structures of the intermediate of the following reaction.

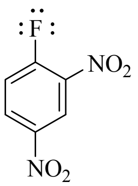
Rxn G



e. Add a line to the energy diagram above for Rxn G.

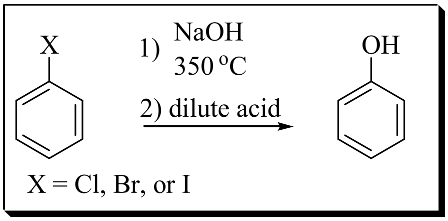
6. S_N1 and S_N2 reactions are dramatically slowed when the leaving group is a moderately poor leaving group such as fluorine. This is not the case for NAS reactions. Construct an explanation for why the rate of NAS is about the same for both of these starting materials. (*Hint*: Look at energy diagrams in the previous CTQ.)





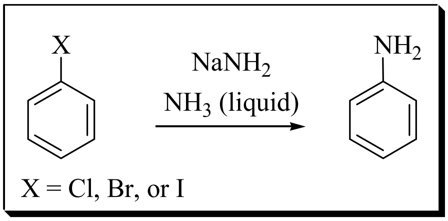
Synthetic Transformations 21.2 and 21.3: Benzyne Reactions

21.2



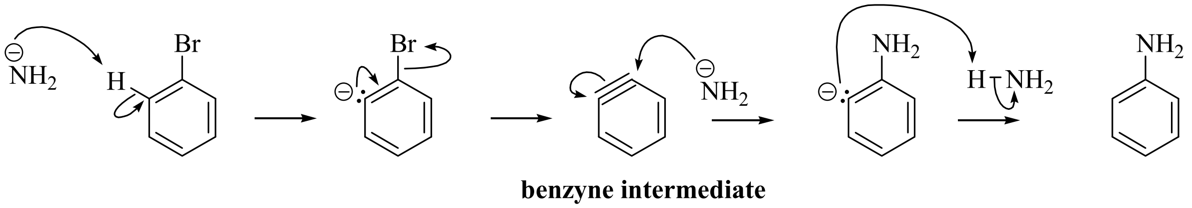
X = Cl, Br, or I

21.3



X = Cl, Br, or I

7. Synthetic Transformations 21.2 and 21.3 are postulated to proceed via the following mechanism, which involves a neutral aromatic intermediate called a benzyne.



a. Construct an explanation for the "yne" ending of the name "benz**yne** intermediate."

b. Construct an explanation for why extreme conditions, either high temperature and a strong base (21.2) or an extremely strong base (21.3), are needed to generate a benzyne intermediate.

c. Exposing *p*-chlorotoluene to $NaNH_2$ under benzyne-forming conditions (liquid ammonia) yields BOTH the *para* and *meta* products. Draw mechanisms for formation of both products, and explain why this observation is strong evidence of a benzyne intermediate (rather than an ordinary addition-elimination like NAS).

8. The following is a summary of how the position and type of substituents on a phenyl ring affect the rate of nucleophilic aromatic substitutionvs. electrophilic aromatic substitution (**NAS vs. EAS**). Match each of the following explanations to the correct row of the table:

Explanations:

- R_w inductively stabilizes **anion** but no resonance stabilization
- R_w deactivates *o/p* positions via resonance (**de**stabilizes **carbocation** intermediate)
- R_w stabilizes **anion** intermediate through resonance
- R_D activates *o/p* positions via resonance (stabilizes **carbocation** intermediate)
- Both R_w's stabilize **anion** intermediate through resonance
- R_D **de**stabilizes **anion** intermediate

Reaction Type	**Group(s) on Ring**	**Product Description**	**Reaction Rate**	**Explanation**
EAS Aromatic ring acts as **nucleophile** intermediate is a **carbocation**	R_w	E^+ adds *m*	Slow	
	R_D	E^+ adds *o/p*	Fast	
NAS Aromatic ring acts as **electrophile** intermediate is an **anion**	R_w *o* or *p* to a LG	Nuc^- subs for LG	Slow	
	Two R_w's *o* and/or *p* to a LG	Nuc^- subs for LG	Fast	
	R_w *m* to a LG	Nuc^- sub for LG (low yield)	Very Slow	
	R_D *o/p* or *m* to a LG	No Reaction	–	

Key:

R_w= a strong electron-withdrawing group such as nitro or an acyl group.

R_D= a strong electron-donating group such as amino or hydroxy group.

E^+ = electrophile

Nuc^- = nucleophile

LG = leaving group

o/p = ortho or *para*

m = meta

9. Read the assigned pages in your text, and do the assigned problems.

The Big Picture

NAS reactions are much less common and versatile than EAS reactions; however, NAS is a good way to generate phenols (Ar-OH) and anilines (Ar-NH_2) [where Ar = aromatic ring]. As shown in Synthetic Transformations 21.2 and 21.3, this can be done from any aryl halide (even without an electron-withdrawing group *ortho* or *para* to the ring).

The reactions in this ChemActivity and the previous one on EAS are often combined to make challenging synthesis problems. Application of the technique called *retrosynthesis* to such problems is showcased in the next ChemActivity.

While NAS and EAS reactions make for interesting synthesis problems, they are also good material for mechanism problems. Be sure to review the mechanisms of these two types of reactions, noting their similarities (both start and end with an aromatic molecule, and the rate of each reaction is dramatically affected by the presence and placement of EWG's or EDG's on the ring), and differences (in EAS the ring is nucleophilic and activated by *ortho* and *para* EDG's while in NAS the ring is electrophilic and activated by *ortho* and *para* EWG's). Note also that in EAS an electrophile substitutes for an aryl H, while in NAS a nucleophile substitutes for an aryl halogen.

Common Points of Confusion

- It sounds simple, but the most common error regarding NAS is that students forget that substitution can occur only if there is a halogen (or halogen-like) leaving group. (Note that substitution always occurs at the carbon attached to the leaving group, except in a benzyne-mediated reaction substitution can occur at the leaving-group carbon or the adjacent carbon.)
- The above bullet also can be stated by saying that in NAS there are no "directing effects" the way there are in EAS unless there are multiple leaving groups to choose from (as in Exercise 3).
- Strangely, in most textbooks, NAS reactions are included as a sub-topic within a chapter entitled Electrophilic Aromatic Substitution. This may contribute to students confusing EAS and NAS.

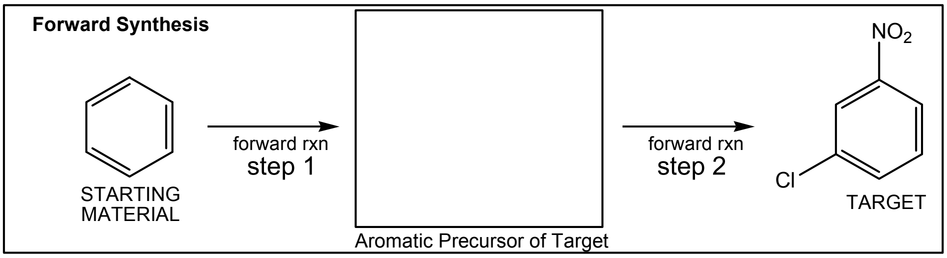
ChemActivity 22: Synthesis Workshop 2

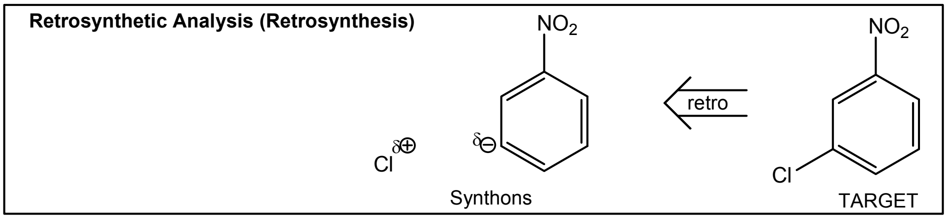
(How can I change an *ortho/para* director into a *meta* director or vice versa?)

Model 1: Review of Synthesis and Retrosynthesis (*See CA 16*)

Often the best way to design a synthesis of a **target** molecule is to mentally pull the target apart into simpler idealized parts (called **synthons**) using a technique called **retrosynthesis.** (See CA 16.)

The target below can be made in two steps from benzene. Forward steps are shown with reaction arrows; a retrosynthetic step is shown with a special **retrosynthetic arrow** (labeled "retro" below).





Critical Thinking Questions

1. This synthesis is simple enough that you may be able to "go forward" and write the reagents for each step over the reaction arrows, but for practice let's think backwards from the TARGET.

   a. (E) In the "Retrosynthetic Analysis" section at the bottom of Model 1, put an **X** through the bond on the target that would give the **synthons** shown.

   b. The **precursors** associated with these synthons are stable organic reagents that behave like the synthons. In the box above the synthons, draw the precursor of the aromatic synthon shown.

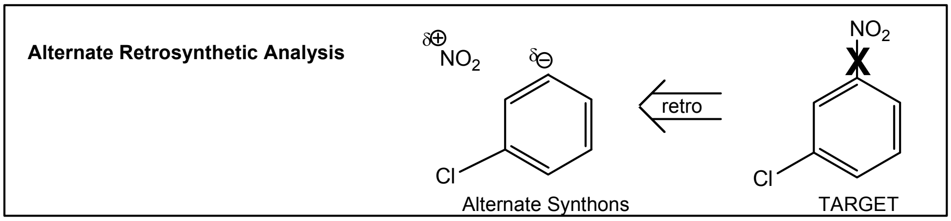
   c. (Check your work.) In an EAS reaction involving nitrobenzene, a carbon *meta* to the NO_2 group will function as the nucleophile. Is this consistent with your answer to part b?

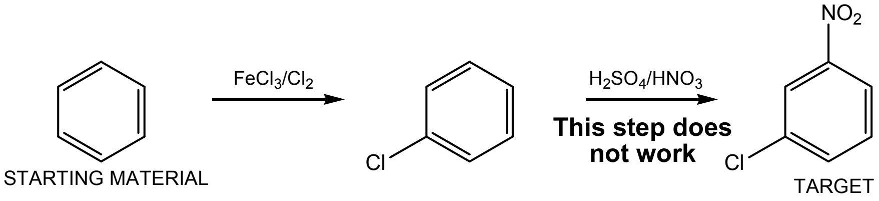
   d. Over the reaction arrow labeled Step 2, write precursors of the synthon Cl^+ (that is, reagents that will act like Cl^+ and transform nitrobenzene into the target, *meta*-chloronitrobenzene).

2. Over the reaction arrow labeled Step 1, write reagents that will accomplish this forward step.

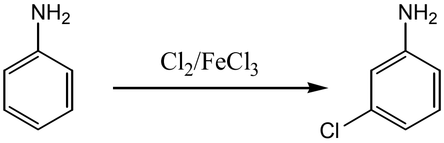
3. In my retrosynthetic analysis of the target in Model 1, when I put an X on the C—Cl bond, I could have decided to draw the synthons with the opposite charges (i.e., $Cl^{\delta-}$ and $C^{\delta+}$). Construct an explanation for why I chose the charge polarization shown rather than the opposite. (*Hint*: Can you cite a reaction in which a carbon on the ring acts as an electrophile and Cl acts as a nucleophile?)

4. A student decides to start a retrosynthetic analysis of this target by putting an **X** on the C—N bond (instead of the C—Cl bond). Explain why the second step in the resulting synthesis fails.





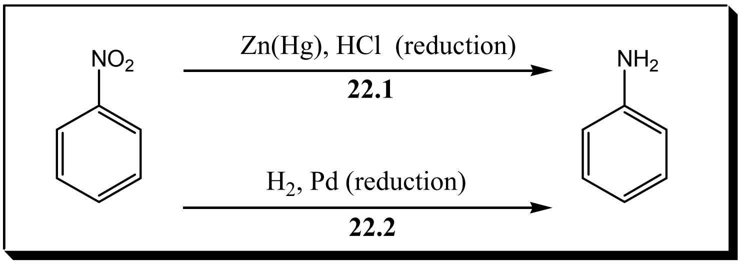
5. A student proposes the following as part of a synthesis. List possible problems with this step.



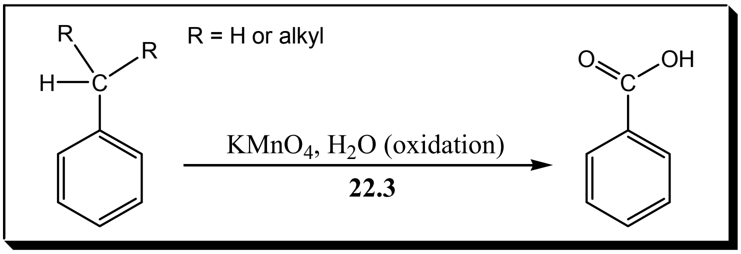
Model 2: Changing an *o/p* to a *m* Director, or Vice Versa

It is sometimes possible to change an *ortho/para* director into a *meta* director, or vice versa. Examples include **Synthetic Transformation 19.7** and the new transformations shown below.

Synthetic Transformations 22.1-22.2



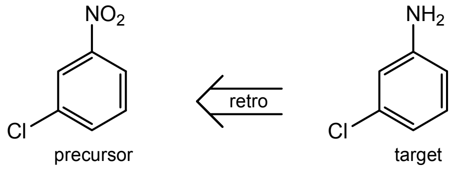
Synthetic Transformation 22.3



Critical Thinking Questions

6. Label the group on each of the four benzene derivatives in Model 2 as "*o/p* director" or "*m* director," as appropriate.

7. In retrosynthesis, a retro arrow can be associated with crossing out a bond (as you did in Model 1) or with a functional group transformation as shown below.

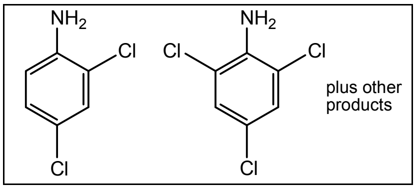


   a. Add a reaction arrow (from left to right) to the step above, and write in reagents that will transform the precursor into the target.

   b. Use retrosynthesis to design a synthesis of the target above, starting from benzene. Be sure to write reagents over each reaction arrow for each forward step.

Model 3: Attenuating the Effects of a Strong Activator *(attenuate = weaken)*

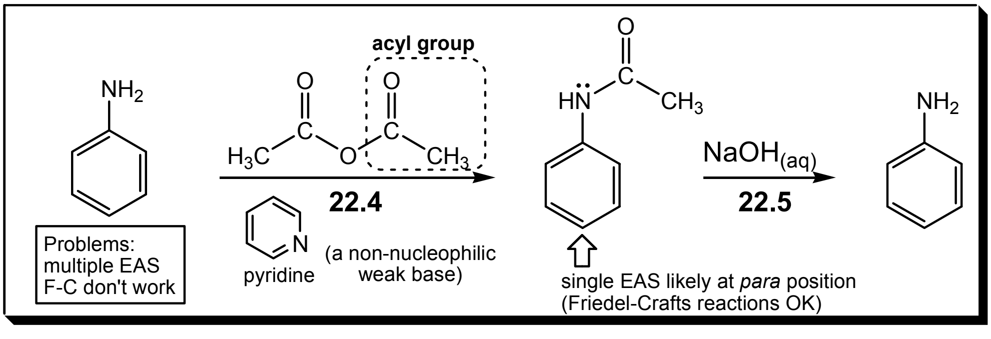
The reaction in CTQ 5 gives a mixture of products including both structures shown at right →



(Check your work.) A complete answer to CTQ 5 cites that NH_2 is such a strong activator that the EAS reaction would be uncontrolled, leading to multiple Cl substitutions.

This and other problems associated with aryl amines (e.g., they do not undergo Friedel-Crafts reactions) can be solved by temporarily substituting an **acyl group** for an H on the N, as shown below.

Synthetic Transformations 22.4 and 22.5: Acylation and de-Acylation of Anilines


NH2
Problems: multiple EAS F-C don't work
acyl group
H3C
O
C
O
O
C
CH3
22.4
pyridine
N
(a non-nucleophilic weak base)
HN
O
C
CH3
single EAS likely at para position (Friedel-Crafts reactions OK)
NaOH(aq)
22.5
NH2

The mechanisms of both these reactions will be covered in the next ChemActivity.

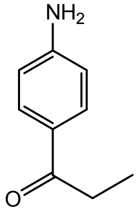
Critical Thinking Questions

8. (E) Circle the **acyl group** on the acylated aryl amine (acylated aniline).

9. Draw a second-order resonance structure demonstrating that the lone pair shown on the N of the acylated aniline is pulled (delocalized) toward the oxygen.

10. Construct an explanation for why, unlike aniline, an acylated aniline can undergo a single controlled EAS reaction, and explain why substitution is favored at the *para* position over the *ortho* position.

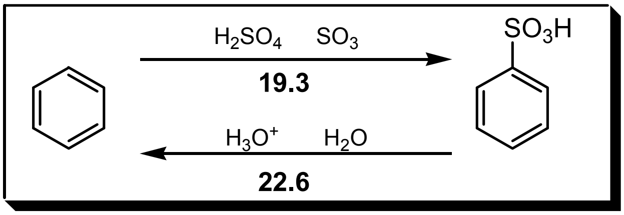
11. Design a synthesis of the following target from benzene.



Model 4: Protecting Groups

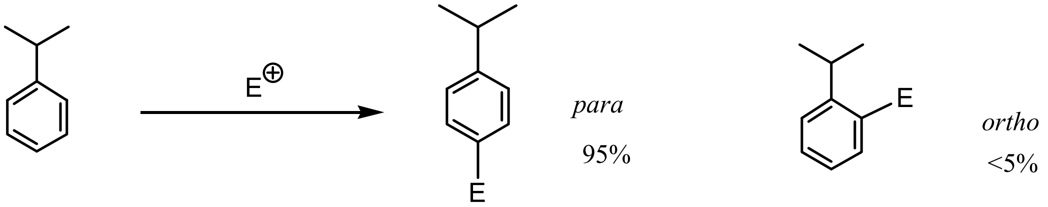
A **sulfonic acid group** can be added or removed from an aromatic ring. This means an SO_3H group can be used to temporarily block a position on an aromatic ring during a synthesis.

Synthetic Transformations 19.3 & 22.6: Sulfonation and de-Sulfonation of Aromatic Rings

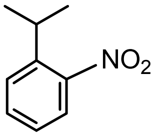


Critical Thinking Questions

12. In EAS involving a bulky substituent (bulky is usually defined as 2° or 3°) the electrophile is directed by steric effects to the *para* position over the *ortho* position (as shown below).



Propose a synthesis from this starting material that gives **primarily the *ortho*-nitro product** shown below. *Hint*: Re-read the underlined statement in Model 4.



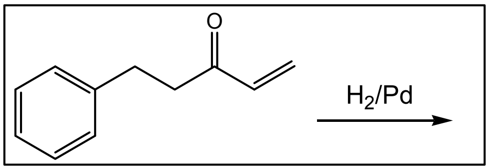
TARGET

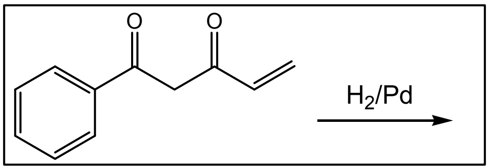
13. Construct an explanation for why the sulfonic acid group in your synthesis in the previous question is said to be used as a "**protecting group**."

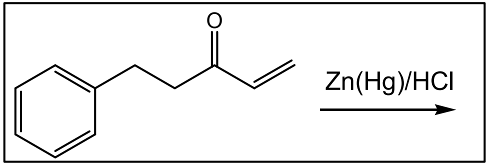
Exercises

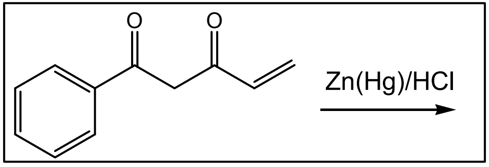
1. *tert*-Butyl benzene does not react with $KMnO_4$. Is this consistent with Synthetic Transformation 22.3? Explain.

2. Review Synthetic Transformation 19.7, and predict the product of each of the following reactions.

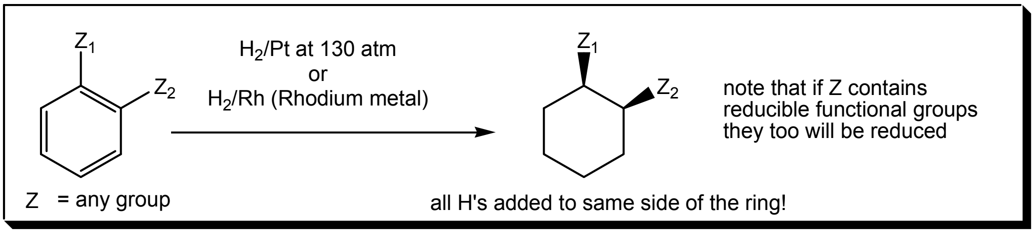








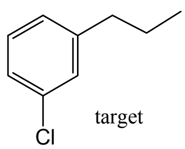
Synthetic Transformation 22.7: Complete Benzene Reduction


Z1
Z2
H2/Pt at 130 atm
or
H2/Rh (Rhodium metal)
Z1
Z2
note that if Z contains reducible functional groups they too will be reduced
Z = any group
all H's added to same side of the ring!

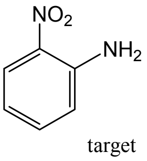
3. Draw the products that result if the starting materials in the previous exercise question are treated with H_2/Pt at high pressure (or H_2 and rhodium metal).

4. Design a synthesis of *n*-propylbenzene from benzene. *Hint*: A one-step synthesis using $CH_3CH_2CH_2Br$ and $AlBr_3$ yields a large amount of isopropylbenzene.

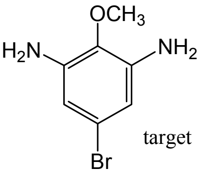
5. Design a high-yield synthesis of each target starting from benzene.



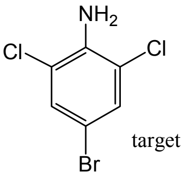
target



target



target



target

6. Make up a synthesis problem that focuses on synthetic transformations involving aromatic molecules. If it is a good synthesis problem, email it to your instructor (write a description of it in words), and there is a chance it will show up on the next quiz.

7. Read the assigned pages in your text, and do the assigned problems.

The Big Picture

Synthesis problems involving aromatic rings usually include EAS reactions. The new reactions in this activity are not EAS reactions, but they can be very useful for directing substituents in an EAS reaction or modifying substituents after they have been added to a ring in an EAS reaction.

This activity also introduces the concept of a temporary group that is used to reduce (attenuate) the reactivity of an aryl amine or block a position on the ring. These are generally called **protecting groups**. We will learn about another, more common, protecting group strategy in a future activity. Protecting groups play a huge role in syntheses performed in the laboratory.

This activity is an opportunity to get the differences between NAS and EAS sorted out and is the last in a series of ChemActivities focusing on aromatic molecules. The next group of ChemActivities will focus on the chemistry of carbonyl compounds.

Common Points of Confusion

Many students consider synthesis to be the most challenging (and frustrating) part of an organic course. The following advice on how to make synthesis less intimidating (and perhaps even fun) was provided at the end of Synthesis Workshop 1 (ChemActivity 16):

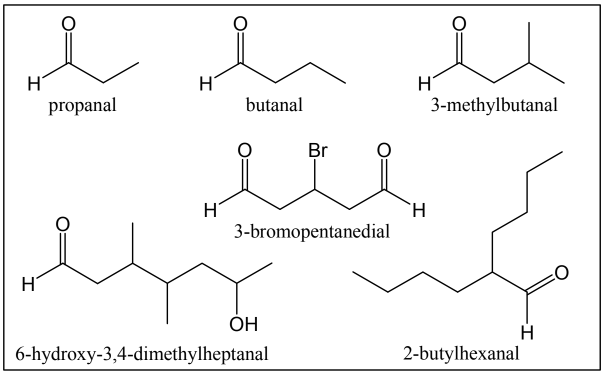
In organic synthesis, as with every topic in this course, the situation is not nearly as bad as you think. Do not let the reputation of this course or your anxiety get in the way of enjoying organic synthesis, one of the most creative and potentially fun challenges you will encounter in all of science.

- **Memorize all the Synthetic Transformations** using the four-note card strategy outlined in the Exercises of ChemActivity 8. You must know these forward and backward. Failure to adequately memorize the Synthetic Transformations is the most common cause of difficulties with synthesis problems.
- Practice doing synthesis problems working both from the starting material forward and, using retrosynthesis, from the target backwards.
- Don’t waste time staring at a blank page. Keep your pencil moving and your brain will follow. Start each synthesis by listing the possible first steps forward from the starting material AND the possible last steps, thinking backwards (retrosynthetically) from the target.
- Many two- to four-step synthesis problems can be solved in the forward direction without using retrosynthesis, but retrosynthesis is an invaluable tool for developing a plan for solving complicated syntheses. If you do not understand the point or methods of retrosynthesis, study Part A of ChemActivity 16 and discuss it with a person who seems to like synthesis.
- Chess masters study games played by other masters to learn common sequences of moves. Study the solutions to synthesis problems to build your repertoire of common sequences of transformations.
- Make up your own synthesis problems, and share them with your study partner.

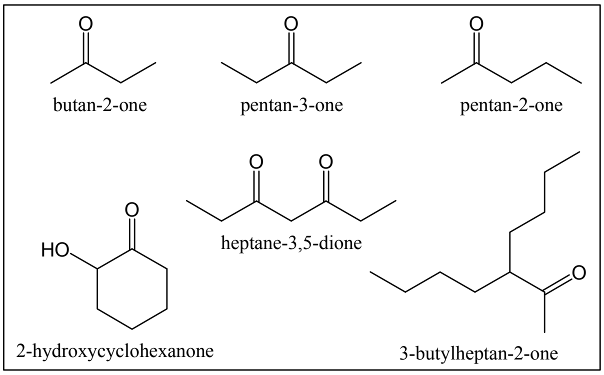
Nomenclature Worksheet 4

CARBONYL COMPOUNDS

Model 1: Aldehyde Nomenclature and Ketone Nomenclature



Aldehydes



Ketones

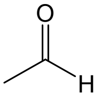
Critical Thinking Questions

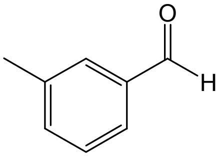
1. (E) Aldehydes and ketones each contain a **carbonyl group**.
    a. Describe the feature(s) that all aldehydes in Model 1 have in common.
    b. Describe the feature(s) that all ketones in Model 1 have in common.
    c. Describe structural difference(s) between an aldehyde and a ketone.

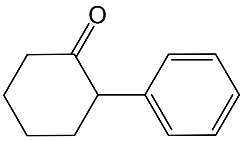
2. To name an aldehyde or ketone you start with the corresponding alkane parent name, remove the final "e" (for example "butane" becomes "butan"), and add a suffix.
    a. (E) What suffix (ending) is added to complete the name of an aldehyde?
    b. (E) What suffix (ending) is added to complete the name of a ketone?

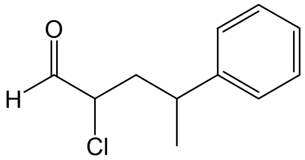
3. Cite an example structure from Model 1 that demonstrates each of the following rules:
    a. The parent chain of an aldehyde must contain the carbonyl carbon.
    b. The parent chain of a ketone must contain the carbonyl carbon.
    c. You always number the parent chain of an aldehyde starting from the carbonyl carbon (even when there is an OH group present). *Note: By convention the "1" is understood and therefore omitted from the name (e.g., butanal, not 1-butanal).*
    d. The carbonyl C of a ketone gets numbering priority over other functional groups, even OH.

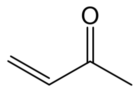
4. Name each of the following compounds.







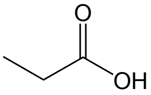




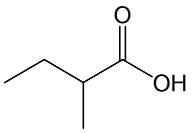
5. Draw each of the following compounds from their names.

a. 2,2-dibromopentanal b. 5-methylcyclopent-2-enone c. 2-(cyclohex-2-enyl)cyclohexanone

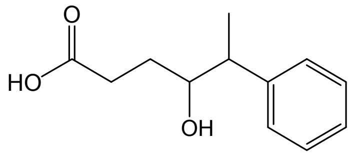
Model 2: Carboxylic Acid Nomenclature



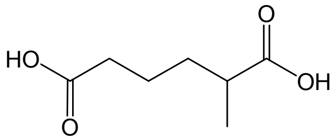
propionic acid



2-methylbutanoic acid



4-hydroxy-5-phenylhexanoic acid



2-methylhexanedioic acid

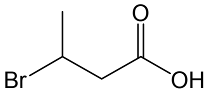
Critical Thinking Questions

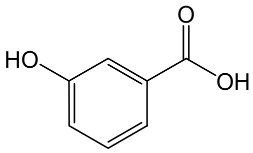
6. (*As with aldehydes and ketones*) To name a carboxylic acid you start with the corresponding alkane parent name, remove the final "e" (e.g., "butane" becomes "butan"), and add a suffix.

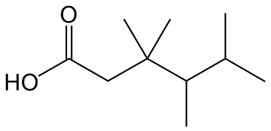
   a. (E) What suffix (ending) is used to name a carboxylic acid?

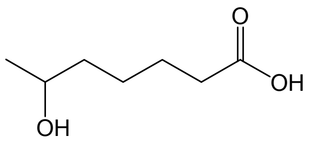
   b. (E) What word comes after the parent+suffix to complete the name of a carboxylic acid?

7. Name each of the following compounds.







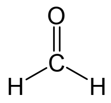


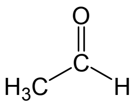
8. Draw each of the following compounds from their names.

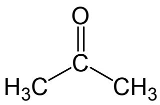
a. ethanoic acid b. 3,3-dimethylbutanoic acid c. 6-cyclohexylhexanoic acid

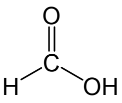
Memorization Task NW3.2: Common Names of Simple Carbonyl Compounds

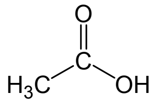
Certain molecules are referred to so often by their common names that you should memorize them:


formaldehyde
(methanal)


acetaldehyde
(ethanal)

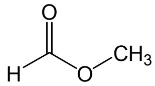

acetone
(2-propanone)

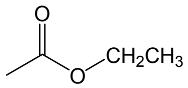

formic acid
(methanoic acid)

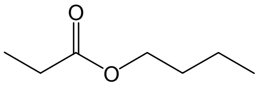

acetic acid
(ethanoic acid)
main component of vinegar

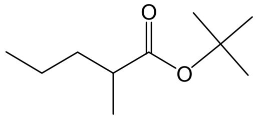
The prefix "**acet–**" is often used to name a two-carbon chain as in **acetic acid** and **acetaldehyde** (**acetone** is an exception to this trend), and the prefix "form–" is often used to name a one-carbon chain as in **formic acid** and **formaldehyde**.

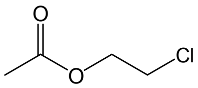
Model 3: Ester Nomenclature


methyl formate
(methyl methanoate)


ethyl acetate
(ethyl ethanoate)


butyl propanoate


tert-butyl 2-methylpentanoate


2-chloroethyl acetate
(2-chloroethyl ethanoate)

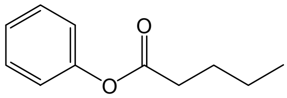
Critical Thinking Questions

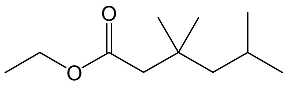
9. Esters are one of class of "**carboxylic acid derivatives**" we will study. Esters are called this because an ester can be "derived from" (made from) a carboxylic acid. Based on the examples in Model 3, describe the structural similarities and differences between esters and carboxylic acids.

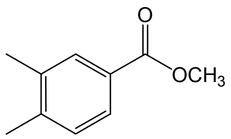
10. (E) Each ester name consists of two words. What does the first word tell you about the structure?

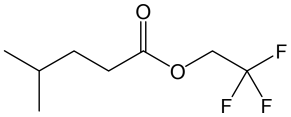
11. The second word in an ester name is generated from the corresponding carboxylic acid name.
    a. What is removed from the carboxylic acid name?
    b. What three letters replace "ic acid" to complete the ester name?

12. Name each of the following compounds.





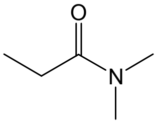




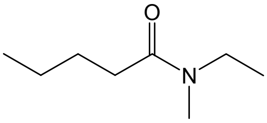
13. Draw each of the following compounds from their names.

a. methyl acetate b. phenyl 3-bromobutanoate c. 2-bromopropyl benzoate

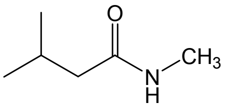
Model 4: Secondary and Tertiary Amide Nomenclature



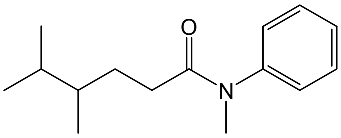
N,N-dimethylpropanamide



N-methyl-*N*-ethylpentanamide



N,3-dimethylbutanamide



N,4,5-trimethyl-*N*-phenylhexanamide

Critical Thinking Questions

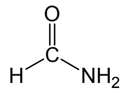
14. Amides (like esters) can be made from carboxylic acids and so are considered another class of **carboxylic acid derivative**. Based on the examples in Model 4, describe the similarities and differences between the structures of amides, esters, and carboxylic acids.

15. Each amide name contains a parent name that tells you the number of carbons in the parent chain. Note that this parent chain must contain the carbonyl group. The parent name is derived by replacing "**oic acid**" in the corresponding carboxylic acid name with "**amide.**"
    - a. Underline the parent name in each name in Model 4.
    - b. Trace the corresponding parent chain on each structure in Model 4, and number the carbons, noting that the carbonyl carbon always gets the number "1".
    - c. Circle each alkyl group (if any) that branches off the parent chain.
    - d. Circle each alkyl group (if any) that is attached directly to the nitrogen.

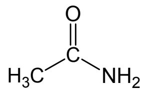
16. For an amide, the names of all the circled alkyl groups are listed before the parent name.
    - a. What information does an italic capital *N* in front of an alkyl group (e.g., *N*-methyl) convey?
    - b. What information does a number in front of an alkyl group (e.g., 3-methyl) convey?

17. Three of the amides in Model 4 are called **tertiary amides** because there are three C's bound to N.
    - a. Which amide in Model 4 is a **secondary amide**?
    - b. Draw and name an example of a **primary amide**.

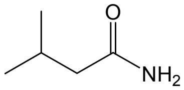
Model 5: Primary Amides



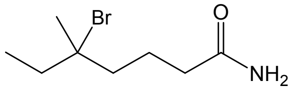
formamide
(methanamide)



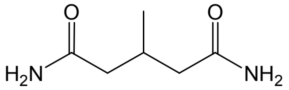
acetamide
(ethanamide)



3-methylbutanamide



5-bromo-5-methylheptanamide



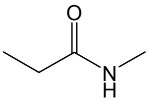
3-methylpentanediamide

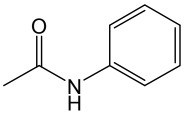
Critical Thinking Questions

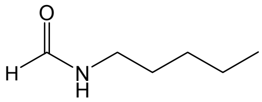
18. Explain why you will never find an italic capital *N* in the name of a primary amide.

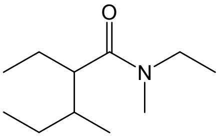
19. Identify the two common names shown in Model 5, and write the carboxylic acid common names from which these amide common names were derived.

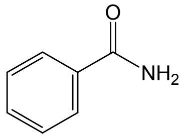
20. Name each of the following compounds.







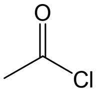




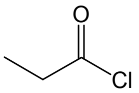
21. Draw each of the following compounds from their names.

a. *N*-methylformamide b. *m*-nitro-*N*-phenylbenzamide c. 3-phenyl-*N*-propylpropanamide

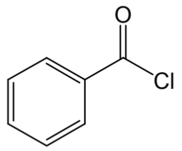
Model 6: Acid Halide Nomenclature



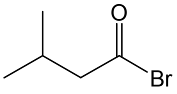
acetyl chloride
(ethanoyl chloride)



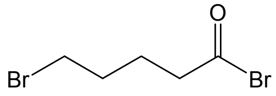
propanoyl chloride



benzoyl chloride



3-methylbutanoyl bromide



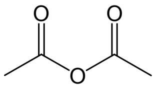
5-bromopentanoyl bromide

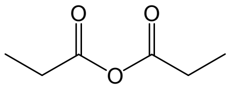
Critical Thinking Questions

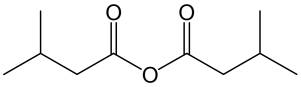
22. Below each acid halide in Model 6, write the name of the corresponding carboxylic acid.

23. Based on the examples in Model 6, construct a set of rules for writing the name of an acid halide from the corresponding carboxylic acid name.

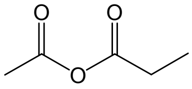
Model 7: Acid Anhydride Nomenclature


acetic anhydride


propionic anhydride


3-methylbutanoic anhydride

Examples of symmetrical acid anhydrides


acetic propionic anhydride

Critical Thinking Questions

24. Draw the structure of acetic acid below the structure of acetic anhydride.

25. Describe the similarities and differences between the structure of a symmetrical acid anhydride and the structure of the corresponding carboxylic acid.

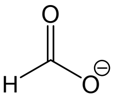
26. Based on the examples in Model 7, construct a set of rules for writing the name of a symmetrical acid anhydride from the corresponding carboxylic acid name.

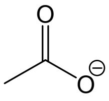
27. Draw the structure of benzoic anhydride.

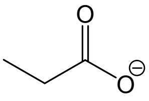
28. Based on the example in Model 7, construct a set of rules for writing the name of an asymmetric acid anhydride from the corresponding carboxylic acid names.

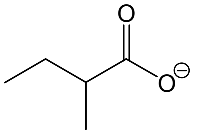
29. Draw the structure of propionic benzoic anhydride.

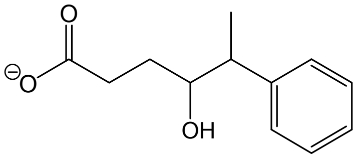
Model 8: Naming the Conjugate Base of a Carboxylic Acid


formate


acetate


propionate


2-methylbutanoate


4-hydroxy-5-phenylhexanoate

Critical Thinking Questions

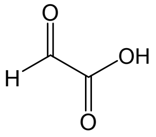
30. Based on the examples in Model 8, construct a set of rules for writing the name of the conjugate base of a carboxylic acid from the corresponding carboxylic acid name.

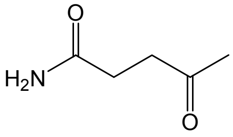
31. For a given carboxylic acid (e.g., acetic acid), the name of its conjugate base (i.e., acetate) is found within the name of one of its derivatives. Draw the structure, and write the name of a derivative of acetic acid (found in this ChemActivity) that contains the word "**acetate.**"

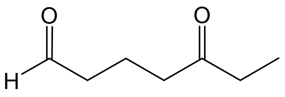
32. Draw the structures of **methyl benzoate** and **benzoate**, respectively. *Warning: Do not confuse the name of an ester with the name of a carboxylate (conjugate base of a carboxylic acid)!*

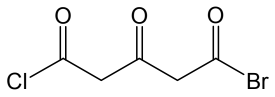
Model 9: "oxo" Nomenclature for Multi-Carbonyl Compounds

In a structure with different carbonyl functional groups, a carbonyl can be named as an **oxo** group.


2-oxoacetic acid


4-oxopentanamide


5-oxoheptanal


5-bromo-3,5-dioxopentanoyl chloride

Critical Thinking Questions

33. Draw each of the following compounds from their names.

a. 2-oxobutanoic acid b. 3,4-dioxopentanoyl chloride c. phenyl 3-chloro-3-oxopropanoate

Exercises

1. Which names in Model 3 are common names, and which are IUPAC names? (The common names shown are used much more frequently than the IUPAC names for these compounds.)

2. Complete the analogy: ester is to alcohol as amide is to ______________________.

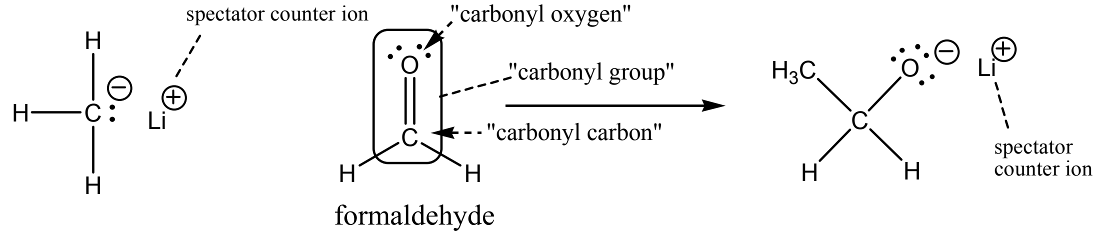
3. Draw the structure that corresponds to each of the following names.
    a. butanal
    b. 2,2-dimethylhexan-3-one
    c. 6-methyl-4-propylheptan-3-one
    d. 2-(2,2-dimethylbutyl)heptanal
    e. 2,6-difluorobenzoic acid
    f. 5,5-diphenylpentanoic acid
    g. 3-chloropentanoyl chloride
    h. cyclobutanone
    i. methyl acetate (or methyl ethanoate)
    j. 4-ethyl-2,3-dimethylhexanamide
    k. acetamide (or ethanamide)
    l. *N*-isopropyl-*N*-propylhexanamide
    m. 3-methylbutan-2-yl propionate
    n. benzyl benzoate
    o. 2,4,6-trimethylbenzyl acetate
    p. 2-phenylacetic anhydride
    q. phenylacetic propionic anhydride
    r. methyl 5-bromo-5-methylheptanoate
    s. disodium 3-methylpentanedioate (a dianion with two Na^+ counterions)
    t. potassium 3-oxohexanoate (an anion with a K^+ counterion)
    u. *tert*-butyl 2-methyl-4-oxobutanoate
    v. pentane-2,4-dione
    w. isopropyl 3-chloro-3-oxopropanoate
    x. *N*-isopropyl-*N*-methyl-2-oxobutanamide
    y. methyl 2-amino-2-oxoacetate
    z. *N,N*,2,2,3,3-hexamethylbutanamide

ChemActivity 23: Addition to a Carbonyl

PART A: NUCLEOPHILIC ADDITION TO A CARBONYL (C=O)

(What is the mechanism by which an aldehyde or ketone can be converted to an alcohol?)

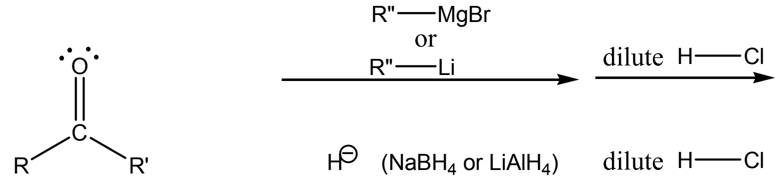
Model 1: Addition of a Lithium (Grignard or Hydride) Reagent to C=O



Review from CA 16: Lithium, Grignard, and **hydride** delivery (e.g., $LiAlH_4$) reagents react quickly and irreversibly with a carbonyl to yield an **alkoxide anion** (the conjugate base of an alcohol).

Critical Thinking Questions

1. Draw a $\delta+$ and a $\delta-$ on appropriate atoms of formaldehyde to show the polarity of the C=O bond.
2. Use curved arrows to show a mechanism for the reaction in Model 1.
3. Draw the alcohol product that results when an aldehyde or ketone is…
   a. treated with a lithium or Grignard reagent and then neutralized with dilute acid.
   b. treated with a hydride (H^-) delivery reagent such as $NaBH_4$ or $LiAlH_4$, then dilute acid.



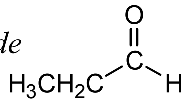
(aldehyde when R or R' = H)

(Check your work.) See Synthetic Transformations 16.4 and 16.6

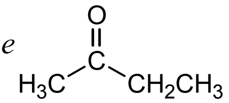
4. According to the following factors, which do you expect to be more susceptible to reaction with a nucleophile, the carbonyl carbon of an aldehyde or a ketone?
   a. Based on steric factors, which is more reactive, **aldehyde C** or **ketone C**?
   b. Based on electronic factors, which is more reactive, **aldehyde C** or **ketone C**?

   (*Hint*: Recall that alkyl groups are electron-donating.)

example of an aldehyde (propanal)



example of an ketone (2-butanone)

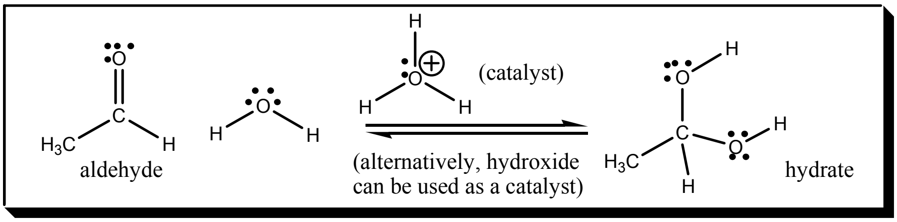


Memorization Task 23.1: Aldehydes are better electrophiles than ketones.
Steric and electronic arguments agree that aldehydes react with nucleophiles better than ketones.

5. (Check your work) Are your answers on the previous page consistent with Memorization Task 23.1?

Model 2: Addition of Water to a Carbonyl (C=O)

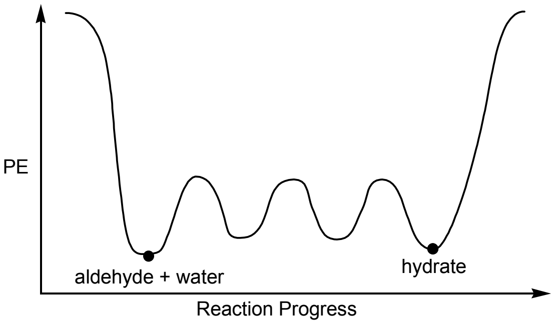
Synthetic Transformation 23.1: Hydrate Formation



In the presence of an acid (H^+) or base (HO^-) catalyst, aldehydes and ketones react with water to form a di-alcohol product called a **hydrate**.

Hydrates are not stable due to the fact that this reaction is easily **reversed**.

A "reversible" reaction is one in which the reverse reaction is downhill or approximately thermoneutral.



Critical Thinking Questions

6. Use curved arrows to construct a mechanism for the reaction in Model 2 such that **no intermediate has a negative charge on H, C or O**. *Hint*: Use the acid catalyst in the first step. (The mechanism of the base-catalyzed reaction is covered in the Exercises for this activity.)

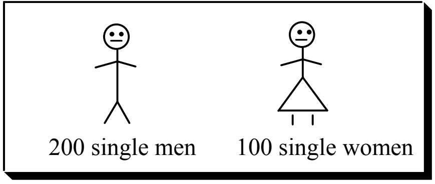
7. (Check your work.) Does your mechanism fit the number of steps shown on the energy diagram?

Model 3A: Singles Dance *circa* 1930

The singles dance where my grandparents met provides a model for understanding how a system at equilibrium responds to stresses like adding more reactants or taking away products.

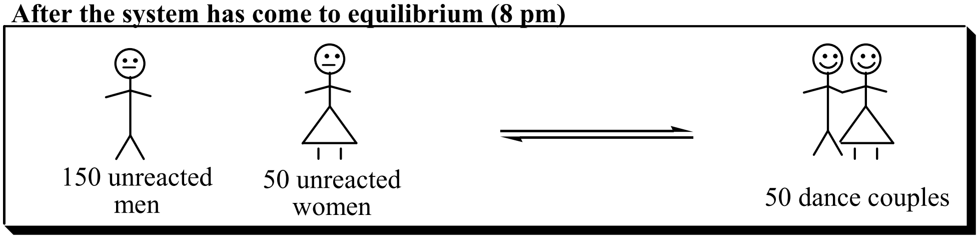
There were about 300 singles at the synagogue that evening: roughly 200 men and 100 women. (Gramps beat the odds!)

Starting Conditions



Because of limited space on the dance floor and teen shyness, by 8 p.m. only 50 male-female dance couples had formed. (For the purposes of this analogy, assume only male-female couples are dancing.)

After the system has come to equilibrium (8 pm)



Critical Thinking Questions

8. For each of the following perturbations (disturbances) of this system at equilibrium, state whether you expect the coupling reaction shown in Model 3A to proceed to the right (forming more dance couples) or to the left (some couples break back into singles).
    a. Someone breaks a glass and one-eighth of the dance floor is closed off.
    b. Several dancing couples leave the synagogue, making more space on the dance floor.
    c. A busload of 100 single men arrive, making the singles area crowded.
    d. A trainload of 1000 single men arrive, making the singles area extremely crowded.

9. Of the last two perturbations, which is likely to generate more couples? Explain your reasoning.

Model 3B: Le Chátelier's Principle

French chemist Henri Louis Le Chátelier (1850-1936) noticed that **a system in equilibrium responds to stress by moving back toward equilibrium**.

Critical Thinking Questions

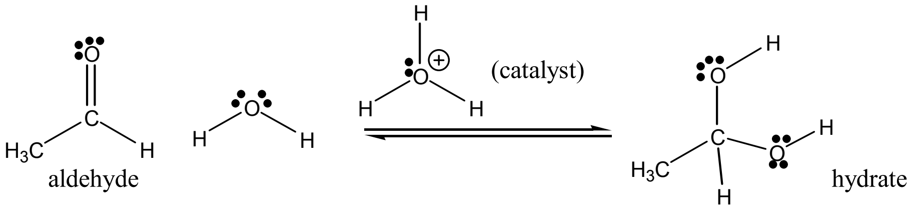
10. Imagine a hypothetical chemical reaction in equilibrium:

$$A + B \rightleftharpoons C + D$$

For each stress, state whether the reaction will go **forward** or **backward** or **neither**.

a.	add more A.	d.	take away some B
b.	add more D	e.	add more A and a similar amount of C
c.	take away some D	f.	add more A and take away a similar amount of D

11. Consider the energy diagram in Model 2. Because the reaction is approximately thermoneutral (neither uphill nor downhill), you would expect a 1:1 ratio of aldehyde to hydrate at equilibrium.



It turns out that we can use Le Chátelier's Principle to control the equilibrium ratio of aldehyde to hydrate by controlling the amount of water. Which of the following actions will shift the equilibrium toward more aldehyde, and which will shift the equilibrium toward more hydrate?

add water or **remove water** Explain your reasoning.

12. Construct an explanation for why it is impossible to isolate a hydrate from solution by distillation. That is, what happens to the hydrate if you boil off the water (solvent) in which it is dissolved?

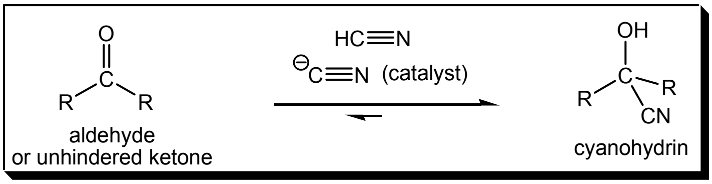
Memorization Task 23.2: Hydrates (and similar adducts) cannot normally be isolated

The nucleophilic addition product of water to a carbonyl compound is unstable and cannot be isolated. This is true for most products made by nucleophilic addition to a carbonyl by the conjugate base of any strong acid (e.g., H_2O, HOR, Cl^-, HSO_4^-, etc.)

Model 4: Addition of Cyanide (H—C≡N) to a Carbonyl (C=O)

In the previous models we explored what happens when you add a very strong base (e.g., Grignard reagent) to a carbonyl and what happens when you add a very weak base (e.g., water) to a carbonyl.

Synthetic Transformation 23.2: Cyanohydrin Formation

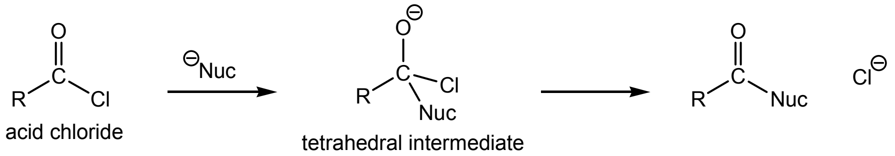


Critical Thinking Questions

13. When you add cyanide (a moderate base and an exceptional nucleophile) to a carbonyl the result is a stable product called a **cyanohydrin**. Construct a mechanism for cyanohydrin formation.

Model 5: Acid Halides (Intro to Nucleophilic Addition-Elimination)

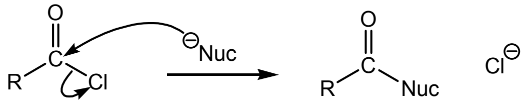
When a nucleophile bonds to a carbonyl carbon that is attached to a good leaving group, it is favorable for the carbonyl to reform via elimination of this leaving group.



Critical Thinking Questions

14. (E) Circle the leaving group on the acid chloride starting material in Model 5.
15. Add curved arrows to Model 5 to show the mechanism of the reaction (all intermediates are shown).

16. What rule does the *incorrect* mechanism at right violate? (Check your work: See Mem. Task 21.1.)

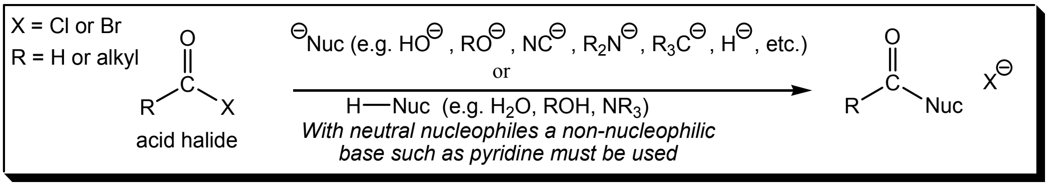


17. For each reagent, predict if the reaction in Model 5 will be downhill from left to right.

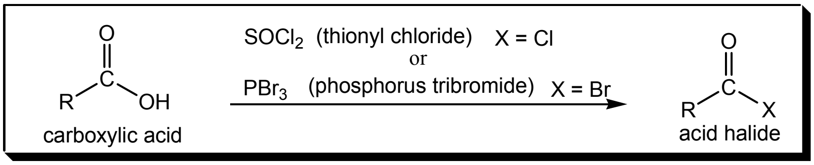
a. NaOH
b. $NaNH_2$
c. C_6H_5MgBr
d. $NaBH_4$ (assume H^-)
e. CH_3CH_2—Li
f. NaBr

18. (Check your work.) Are your answers above consistent with the fact that acid chlorides rapidly and irreversibly form addition-elimination products with all the nucleophiles above except bromide?

Synthetic Transformation 23.3: Acid Halide Reaction (Nucleophilic Acyl Substitution)


X = Cl or Br
R = H or alkyl
O
C
R
X
acid halide
⊖Nuc (e.g. HO⊖, RO⊖, NC⊖, R₂N⊖, R₃C⊖, H⊖, etc.)
or
H—Nuc (e.g. H₂O, ROH, NR₃)
With neutral nucleophiles a non-nucleophilic base such as pyridine must be used
O
C
R
Nuc
X⊖

Synthetic Transformation 23.4: Acid Halide Preparation from Carboxylic Acids


O
C
R
OH
carboxylic acid
SOCl₂ (thionyl chloride) X = Cl
or
PBr₃ (phosphorus tribromide) X = Br
O
C
R
X
acid halide

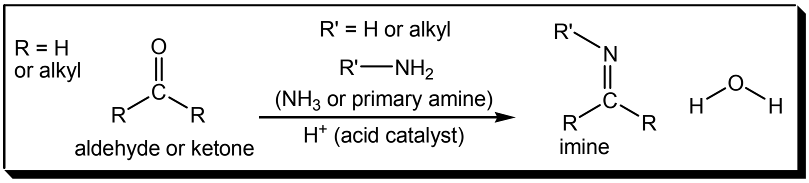
Note: $SOCl_2$ and PBr_3 also can convert an alcohol to an alkyl halide (See Synth. Transf's 13.2 and 13.3.)

PART B: NUCLEOPHILIC ADDITION-ELIMINATION

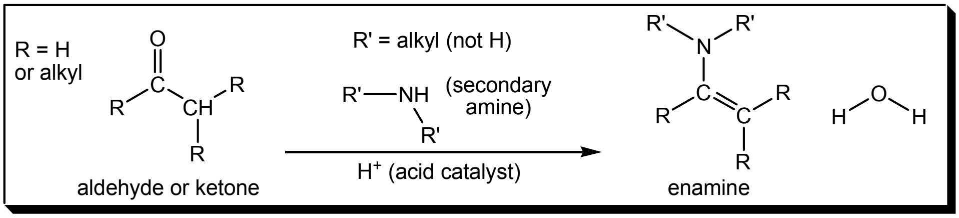
(What is the mechanism of imine, enamine and acetal formation?)

Model 6: Amine Addition-Water Elimination (Imines and Enamines)

Synthetic Transformation 23.5: Imine Formation



Synthetic Transformation 23.6: Enamine Formation

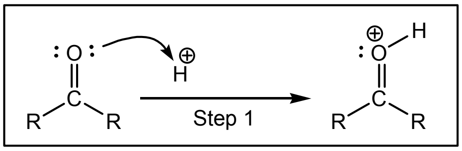


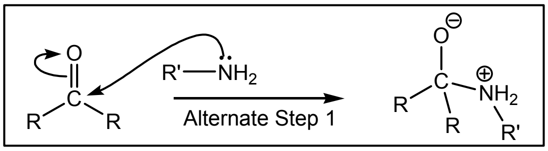
Critical Thinking Questions

19. (E) What is the difference between **imine**-forming reagents and **enamine**-forming reagents?

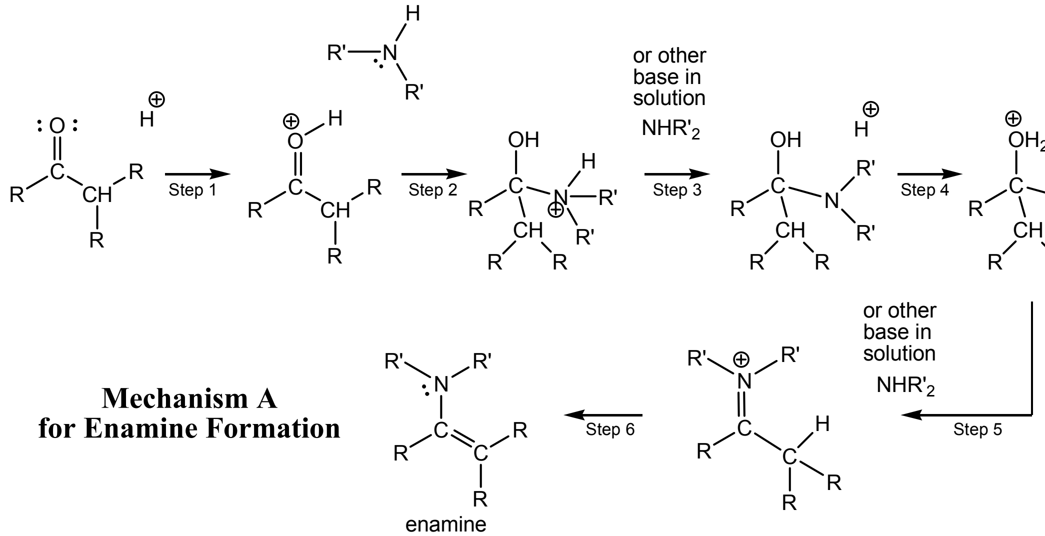
20. Devise a five-to-six step mechanism for Synthetic Transformation 23.5. *Hint*: Recall that an OH group can be protonated with acid to make it into a good leaving group (water).

21. (Check your work.) Either of the following is an acceptable first step for the reactions in Model 6. Check to make sure your mechanism above employs one of these as its first step.





22. The following is an incomplete mechanism for Synthetic Transformation 23.6 (enamine formation).

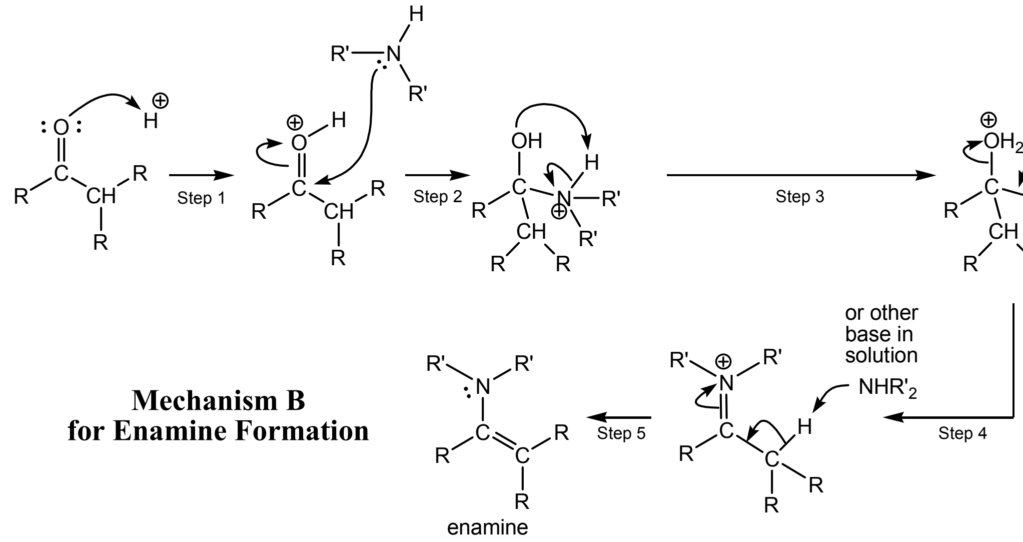


Mechanism A for Enamine Formation

a. Complete the mechanism above by adding curved arrows. (All intermediates are shown.)

b. (Check your work.) Except for the last step, enamine formation is identical to imine formation. Note any differences between this and your imine mechanism on the previous page.

23. Mechanism B (below) is yet another alternate acceptable mechanism for enamine formation.



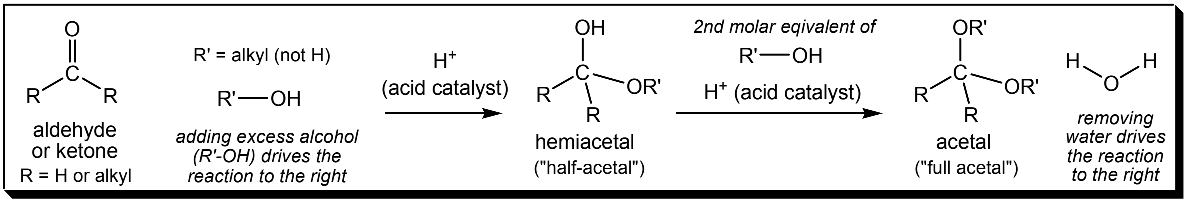
Mechanism B for Enamine Formation

a. Where does Mechanism B differ from Mechanism A?

b. (Check your work.) Step 3 in Mechanism B accomplishes the same thing as Steps 3 *and* 4 in Mechanism A. Construct an explanation for why Step 3 in Mechanism B is called an **intramolecular proton transfer**. *(In this case, intramolecular proton transfer is unlikely because it would require a highly strained four-member ring transition state.)*

Model 7: Alcohol Addition-Water Elimination (Hemiacetals & Acetals)

Synthetic Transformation 23.7: Hemiacetal and Acetal Formation


aldehyde or ketone
R = H or alkyl
R' = alkyl (not H)
R'—OH
adding excess alcohol (R'-OH) drives the reaction to the right
H+ (acid catalyst)
hemiacetal ("half-acetal")
2nd molar eqivalent of R'—OH
H+ (acid catalyst)
acetal ("full acetal")
removing water drives the reaction to the right

Critical Thinking Questions

24. (E) Acetal formation is neither uphill nor downhill in terms of energy. According to Model 7, what are two ways to drive this reaction toward acetal formation (even though it is not downhill)?

25. Explain why both of these actions promote acetal formation.

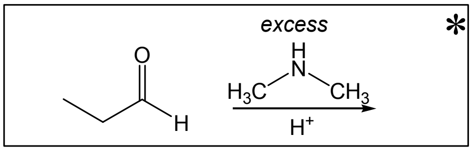
26. Show the mechanism of the first half of Model 7 (from aldehyde/ketone → hemiacetal).

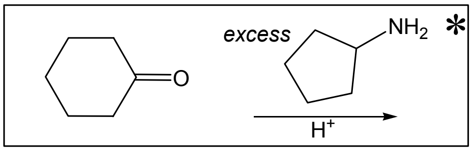
27. (Check your work.) Hemiacetal formation is nearly identical to hydrate formation shown in Model 2, except ROH is used in place of HOH. Check your mechanisms above against the one in CTQ 6.

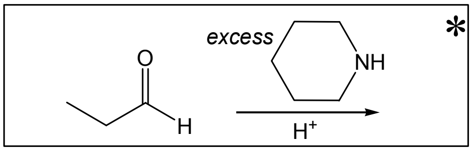
28. Show the mechanism of the second step in Model 7, formation of an acetal from a hemiacetal.

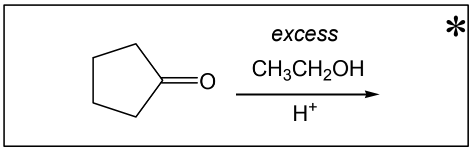
29. Draw the end product(s) of each reaction.

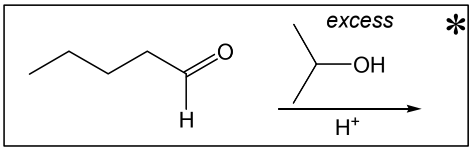
For the first seven reactions with an * ***assume water is distilled (removed) from the product mixture during the reaction***.

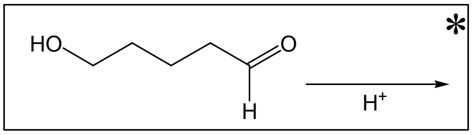




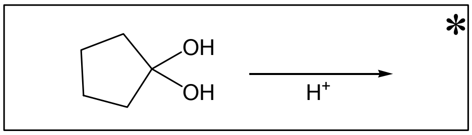


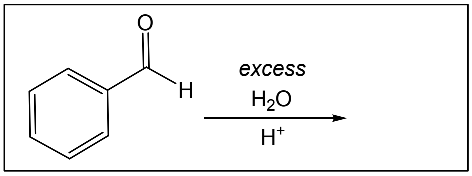


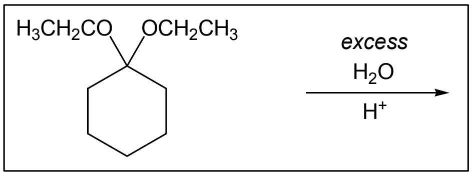




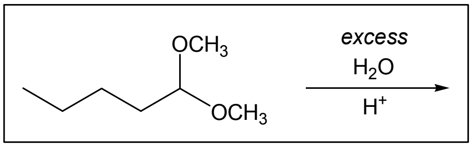
Hint: the END product is a cyclic hemiacetal



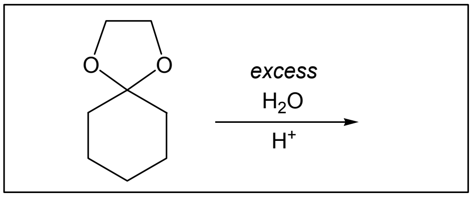




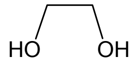
assume ethanol is removed from the product mixture during the course of the reaction



assume methanol is removed from the product mixture during the course of the reaction



hint: one of the products is

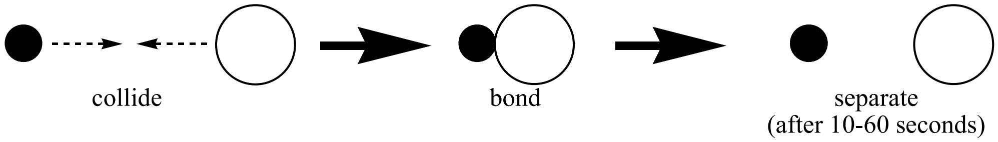


PART C: CYCLIC ACETAL PROTECTING GROUPS

(How can a cyclic acetal be used as a protecting group?)

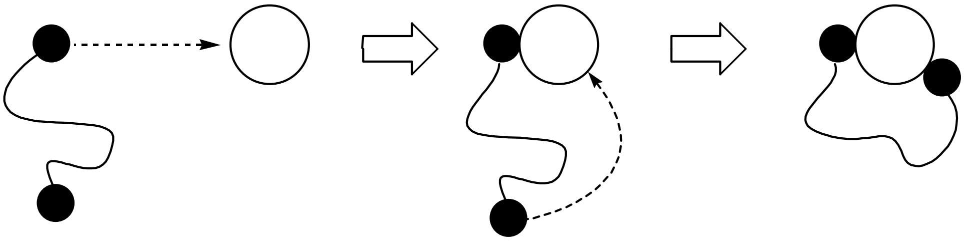
Model 8: White and Black Balls in a Box

Consider a hypothetical box with black and white balls bouncing rapidly around with no gravity or air. When two balls of opposite color collide they tend to stay bound together for 10 to 60 seconds.

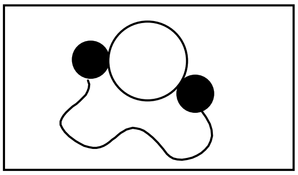


Critical Thinking Questions

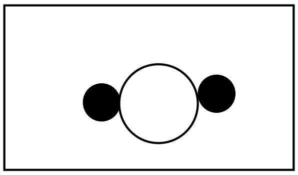
30. If we permanently tether two of the black balls together with a short cord, we find that once one of the two black balls is bound to the white ball, within 1 second the other black ball has a very high probability of also binding the white ball. Construct an explanation for this observation.



31. Construct an explanation for why the three balls on the left are much more likely to stay near each other for a long time than the three balls on the right. (*Hint*: Think about what happens in each case when one of the black balls "lets go" from the white ball.)



more stable
(3 balls tend to stay in the same vicinity)



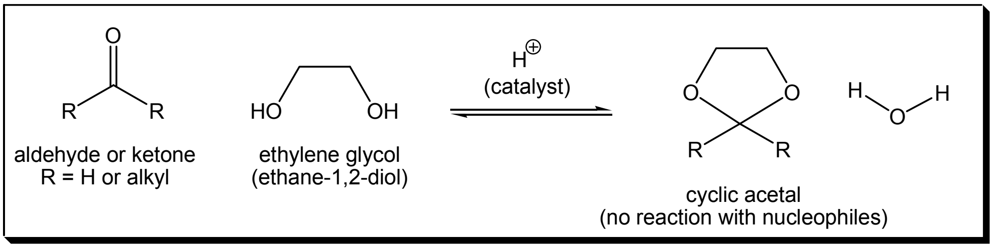
less stable
(3 balls will soon go their separate ways)

intramolecular reaction = a reaction between two parts of the same molecule

Two functional groups in an intramolecular reaction are usually connected by a carbon chain. Such groups are much more likely to react than functional groups on separate molecules because tethered functional groups are more likely to collide with one another (as in the ball example above).

Model 9: Cyclic Acetal Protecting Groups

Synthetic Transformation 23.8: Protection of a Carbonyl Against Nucleophiles

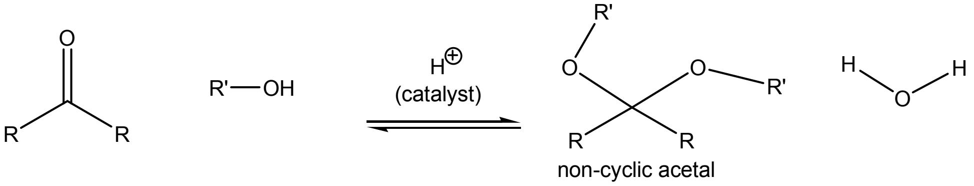


The mechanism of this reaction is explored in the Exercises for this ChemActivity

- Cyclic acetals are very stable in the presence of most bases and nucleophiles (without acid).
- Treatment of a cyclic acetal with acid and excess water generates the original aldehyde or ketone.

Critical Thinking Questions

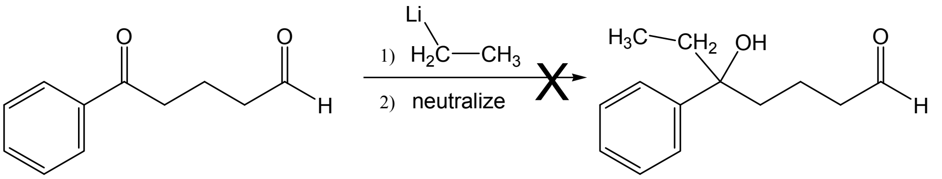
32. Construct an explanation for why a cyclic acetal (above) **forms more readily** and is **more stable** than a normal, noncyclic acetal (shown below). *Hint*: Look back at the previous page.



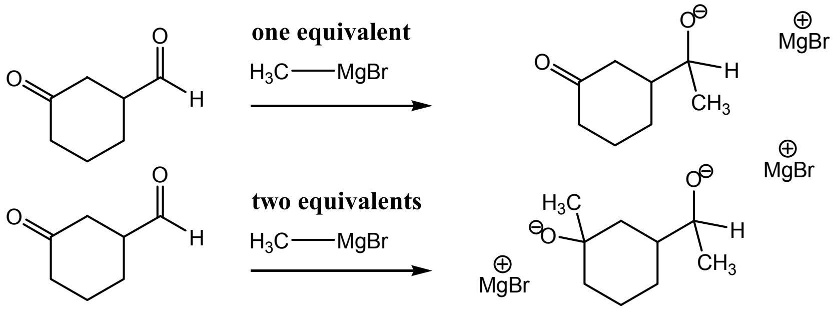
33. (E) The reaction in Model 9 is neither uphill nor downhill. How can you drive this reaction…
    a. to the right, producing a high yield of cyclic acetal?
    b. to the left, producing a high yield of the aldehyde or ketone starting material?

34. (E) According to Model 9, which is more susceptible to reaction with a nucleophile (e.g., RNH_2, H_3C-Li, RC≡CNa, KC≡N, etc.), **an aldehyde or ketone** or a **cyclic acetal** (circle one)?

35. Explain why the following reaction will NOT give a significant yield of the target shown, and draw the nucleophilic addition product that will form. (*Hint*: See Mem. Task 23.1.)



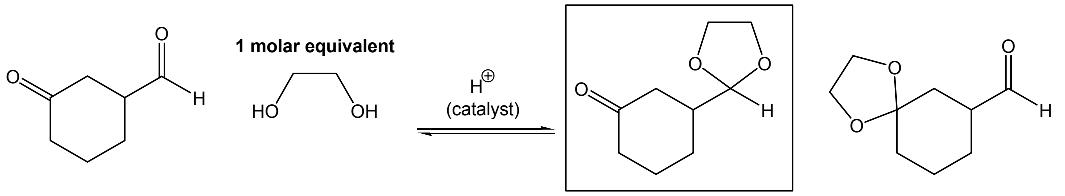
Model 10: Reactivities of Aldehydes versus Ketones



Critical Thinking Questions

36. Based on the reactions in Model 10, which is **more reactive** toward nucleophilic addition, an **aldehyde carbonyl** or a **ketone carbonyl** (circle one)?

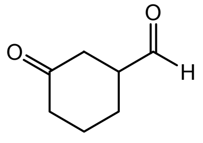
37. Explain why the product in the box forms almost exclusively under these conditions.



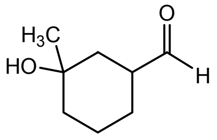
major product

water is distilled from the product mixture to drive the reaction to completion

38. Design a way to accomplish the following synthesis (from the previous page). *Hint*: The structure in the box above is formed during this synthesis.

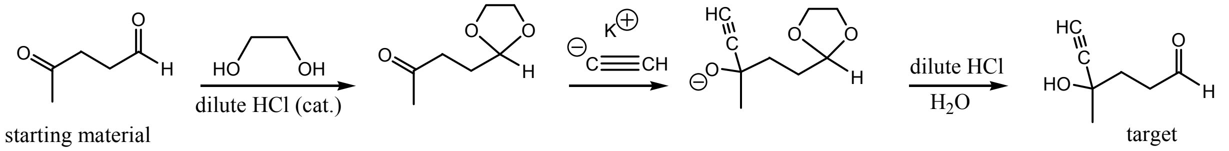


starting material



target

39. Shown below is a successful synthesis of a similar target molecule. Construct an explanation for why the cyclic acetal formed in the first step can be considered a **protecting group** in this synthesis.



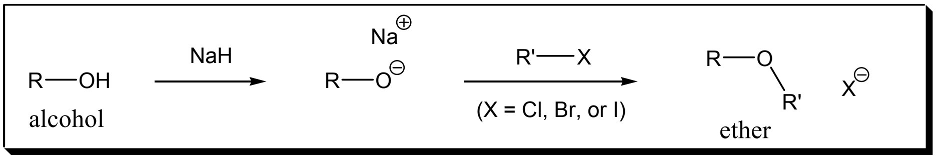
Term Introduction: Protecting Groups

A protecting group is a **removable group that prevents an unwanted reaction** in one part of the molecule while desired chemistry is taking place on another part. At the end of the desired reaction, the protecting group must be able to be removed.

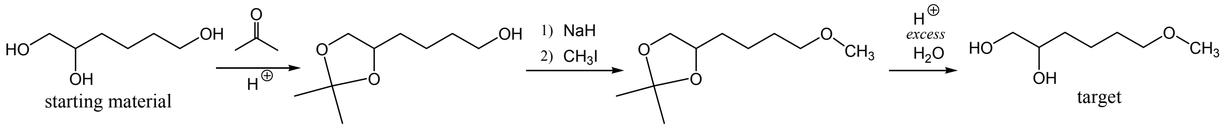
40. Is your answer to the previous question consistent with the Term Introduction section above?

41. The following reaction is commonly referred to by the name of its inventor, Alexander Williamson (1824-1904). The mechanism of this reaction is an acid-base reaction followed by an S_N2 reaction. Identify the acid, the base, the nucleophile and the electrophile.

Synthetic Transformation 23.9: Williamson Ether Synthesis



42. The following is an alternate use of a cyclic acetal as a protecting group.



a. Identify the cyclic acetal protecting group, and circle the functional group(s) in the starting material that the cyclic acetal protects.

b. From what reagent does the cyclic acetal protect these functional groups?

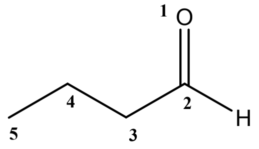
c. What side product(s) might form if the starting material were treated directly with NaH, then CH_3I (without using the protecting-group strategy outlined above)?

PART D: ADDITION TO α,β-UNSATURATED CARBONYLS

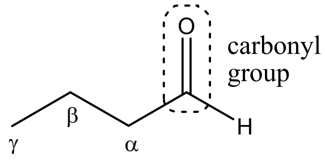
(What is the difference between a **1,4-addition** and a **1,2-addition**?)

Model 11: Systems for Naming Positions on a Carbonyl Compound

An often-used numbering system for carbonyl compounds places a "1" on the oxygen, and a "2" on the carbonyl carbon. Carbons on the chain are numbered starting with "3" as shown at right. *(Note that these numbers do not correspond to the numbering system used for IUPAC naming.)*



Another way of naming positions on a carbonyl compound uses the *Greek* letters α, β, γ, δ, etc. to label the carbons next to, but not part of, the carbonyl group (C=O), as shown at right.



Critical Thinking Questions

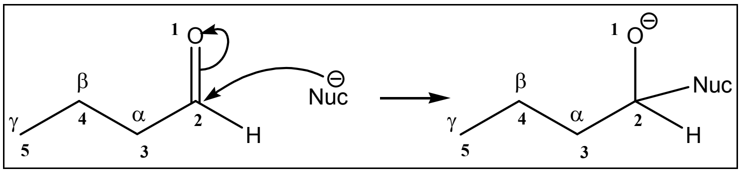
43. (E) Draw an example of an **α,β-unsaturated aldehyde** (an aldehyde with a double bond between the α and β carbons).

44. (E) According to the 1, 2, 3, 4 numbering system for carbonyl compounds described above, where are the double bonds in your **α,β-unsaturated aldehyde**? (circle all that apply) Between the…

1 & 2 positions   2 & 3 positions   3 & 4 positions   4 & 5 positions

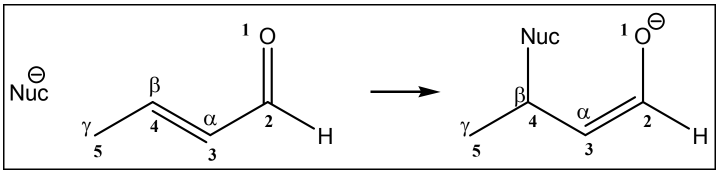
Model 12: Nucleophilic Addition to a Carbonyl at the 2 vs. 4 Position

With ordinary carbonyl compounds, a nucleophile will bond to the carbonyl carbon (also called the "2" position), as shown at right.



It turns out that **α,β-unsaturated carbonyl compounds** react differently.

For reasons we will explore later, most nucleophiles bond to the **β** or "**4**" position of an α,β-unsaturated carbonyl compound, as shown at right.



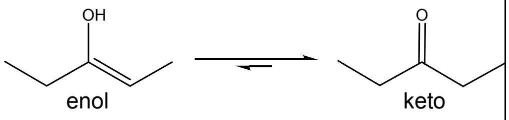
Critical Thinking Questions

45. Add curved arrows to Model 12 to depict electron changes in the (one-step) reaction involving the α,β-unsaturated aldehyde.

Memorization Task 23.3: Enol and Enolate

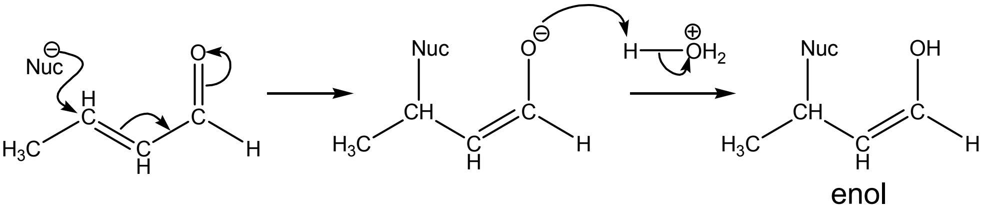
(*Review)* A vinyl alcohol is termed an **enol**. Enols (except phenols) spontaneously convert to their **keto** form.

The conjugate base of an enol is called an **enolate**.



46. All enolates are resonance-stabilized. Identify the enolate in Model 12, and draw its other important resonance structure.

47. The following is one possible way to depict protonation of the enolate from Model 12.



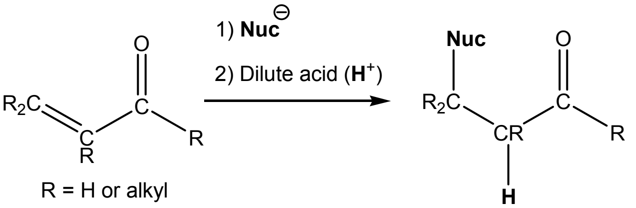
a. The enol shown above is NOT observed in this reaction. Draw the keto form that *is* observed.

b. Number the oxygens and carbons on the enol and keto forms above according to the 1, 2, 3, 4, numbering strategy described in Model 11.

c. A student suggests that this overall transformation should be called a 3,4-addition of H and a Nucleophile. Explain the (very solid) reasoning behind this suggestion.

d. Construct an explanation for why this overall transformation is called (by organic chemists) 1,4-addition of H and a Nucleophile (instead of 3,4-addition).

Synthetic Transformation 23.10: 1,4-Addition to an α,β-Unsaturated Carbonyl



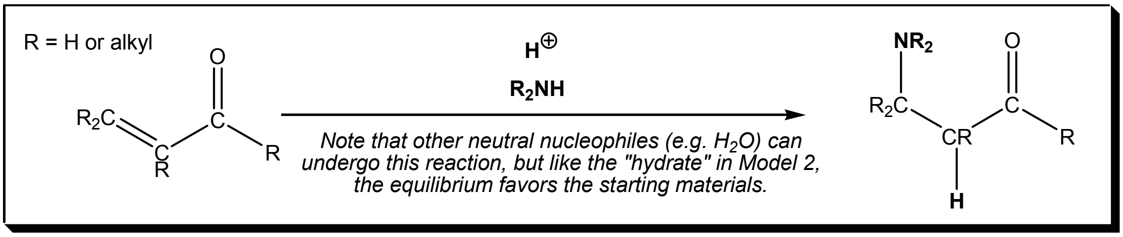
$Nuc^{\ominus}$ = $NC^{\ominus}$, $RS^{\ominus}$, and $C^{\ominus}$ nucleophiles

EXCEPT...

Grignards, lithium reagents, and $RC{\equiv}C^{\ominus}$
(which all undergo 1,2-addition instead of 1,4-addition)

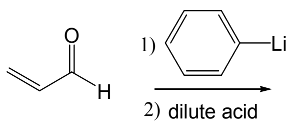
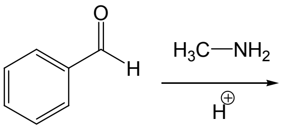
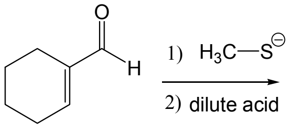
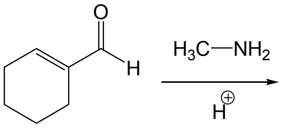
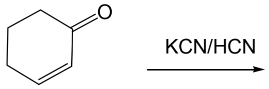
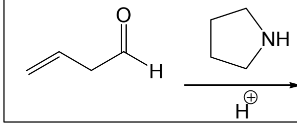
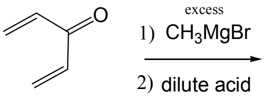
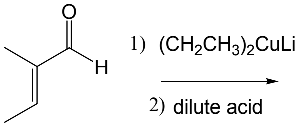
Note that LiR_2Cu reagents undergo 1,4-addition

Synthetic Transformation 23.11: 1,4-Addition of an Amine to an α,β-Unsaturated Carbonyl



Note that other neutral nucleophiles (e.g. H_2O) can undergo this reaction, but like the "hydrate" in Model 2, the equilibrium favors the starting materials.

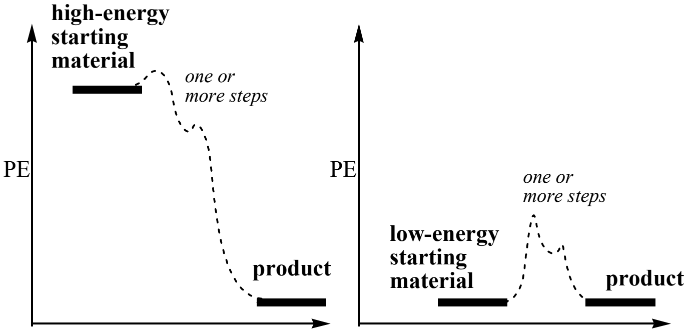
48. Use Synthetic Transformations 23.10 & 23.11 to predict the major product of each reaction below.

49. (Check your work.) Construct an explanation for why, in the top right reaction above, the amine bonds to the carbonyl carbon (giving an imine) instead of the β carbon (as in the reaction below it).

Model 13: Reversible or Irreversible?

A reaction is considered **irreversible** if the reverse reaction is steeply uphill in energy.



Critical Thinking Questions

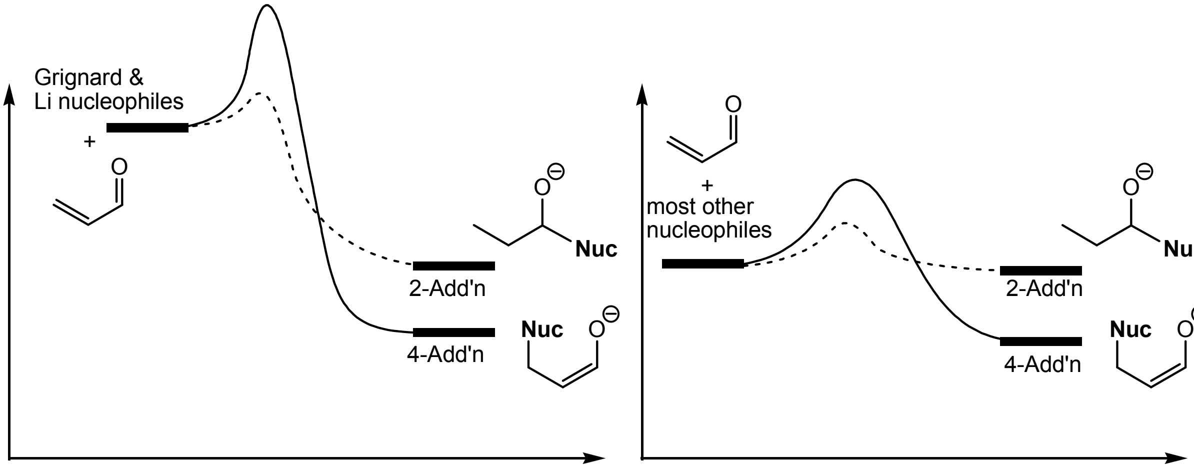
50. Label one energy diagram in Model 13 "irreversible" and the other "reversible."

Model 14: Why 1,2-Addition vs. 1,4-Addition

Memorization Task 23.4: Kinetic versus Thermodynamic Products

The **kinetically favored product** is the product that forms most quickly (lower activation barrier).

The **thermodynamically favored product** is the product that is lower in potential energy.



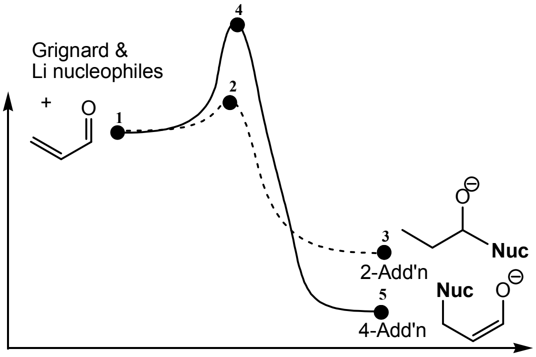
Critical Thinking Questions

51. For the two energy diagrams in Model 14, circle the kinetically favored product and put a box around the thermodynamically favored product.

52. For each energy diagram, which product is most likely to form first and fastest?

53. On the energy diagram on the right in Model 14, trace the path of an α,β-unsaturated carbonyl compound that first becomes a 2-addition product, and then reverts (perhaps several times) back to starting material, only to eventually become a lower-energy 4-addition product.

54. Construct an explanation for why a high-energy nucleophile (such as Grignard or Li reagent) **cannot** reach the 4-addition product by the following path:
1 → 2 → 3 → 2 → 1 → 4 → 5
whereas low-energy nucleophiles *are* able to follow such a path to the 4-addition product.

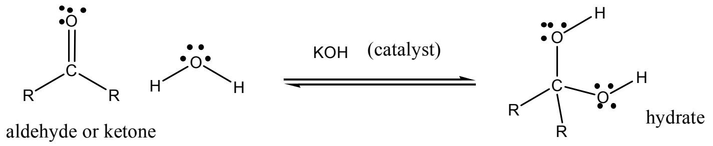


55. Construct an explanation for why high-energy nucleophiles such as Grignard and lithium reagents tend to form 1,2-addition products with α,β-unsaturated carbonyl compounds while milder nucleophiles (including lithium dialkyl cuprates) tend to form 1,4-addition products.

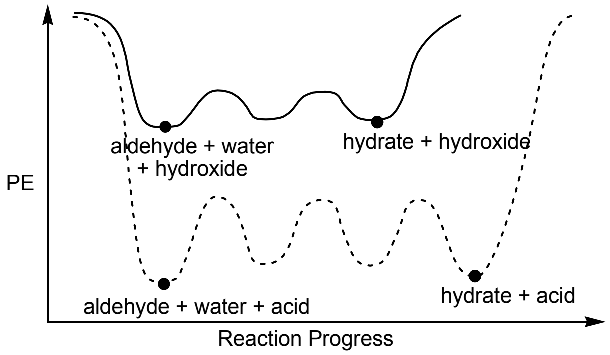
Exercises for Part A:

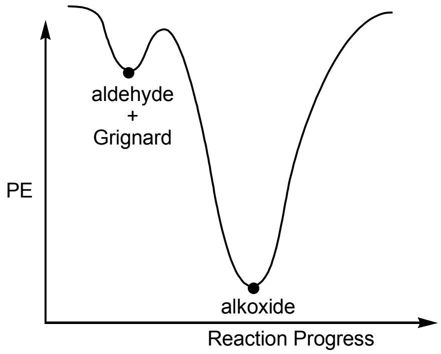
1. The first intermediate in the reaction in CTQ 6 has two resonance forms. Draw the other resonance structure of this intermediate.

2. Devise a mechanism for base-catalyzed hydrate formation.



3. Consider the following reaction profile for base-catalyzed hydrate formation (drawn on the same scale as the reaction profile for acid-catalyzed hydrate formation).





a. (Check your work.) Does the reaction profile fit your mechanism? Explain your reasoning.

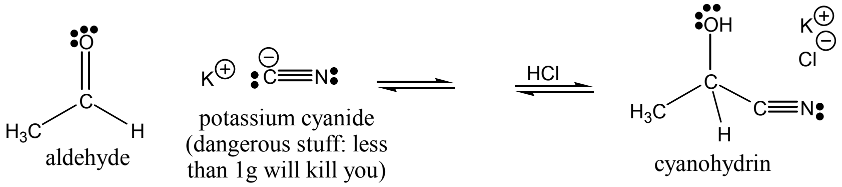
b. Compare the two reaction profiles on the left to the one on the right for reaction of an aldehyde with a Grignard, and construct an explanation for why only the reaction with the Grignard is steeply downhill (exothermic).

c. Construct an explanation for why the two energy profiles on the left are considered "reversible" while the one on the right is considered "irreversible."

4. The reagent sodium borohydride ($NaBH_4$) reacts exactly the way you would expect H^- to react (H^- is a very strong base and is high in energy like a Grignard or lithium reagent). Given this, predict the product that results when butanal is treated with $NaBH_4$ followed by dilute HCl.

5. What reagents could you use to convert this alcohol back to butanal? *Hint*: The sodium borohydride reaction in the previous Exercise is NOT reversible and is considered a reduction of butanal.

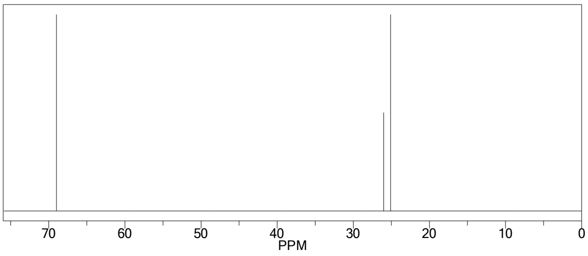
6. Construct a mechanism for the following reaction.

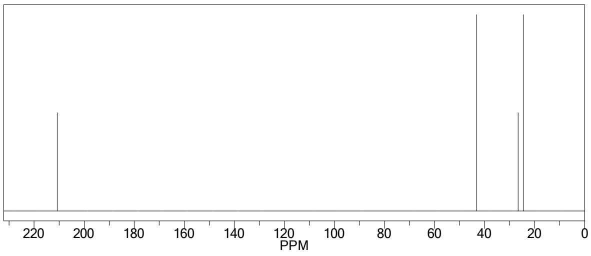

aldehyde
potassium cyanide (dangerous stuff: less than 1g will kill you)
HCl
cyanohydrin

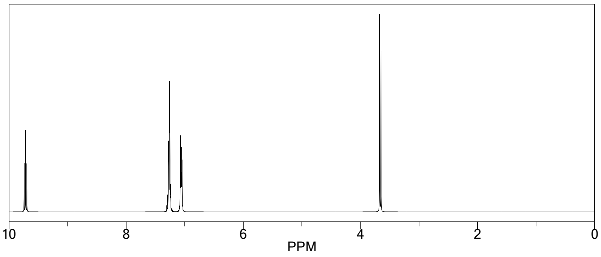
7. Review and memorize the following facts about NMR and of aldehydes and ketones, and use this information to match each spectrum to the correct structure. (Each spectrum is of a different compound).

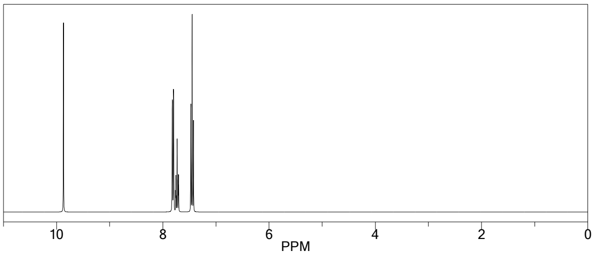
   a. In H^1 NMR, an aldehyde H shows up near 10ppm (to the far left, also called "downfield").

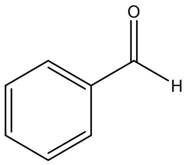
   b. In C^{13} NMR the carbonyl C of an aldehyde or ketone appears above 200ppm.

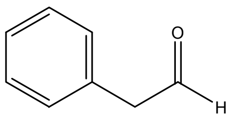


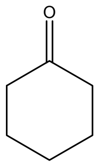


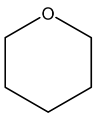








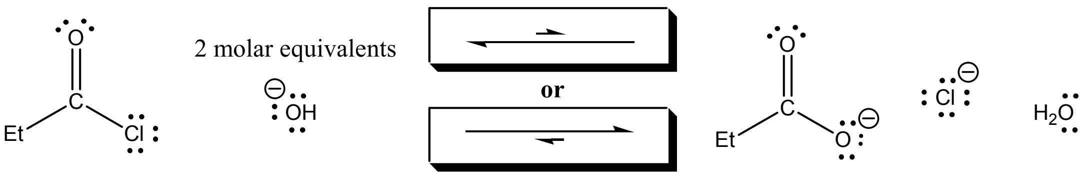




8. Use the following information about IR of aldehydes and ketones to predict which of the carbonyl compounds in the previous question will have the highest frequency carbonyl IR absorption. Recall that wavenumbers (cm^{-1}) are proportional to frequency.

   C=O stretch absorption band on an IR spectrum usually is found between 1660-1770cm^{-1}. The exact location is determined by what kind of functional group and conjugation. In general, aldehyde C=O appear at higher frequency than ketone C=O, and a C=O conjugated to a benzene ring comes at a higher frequency than a C=O conjugated to an ordinary π bond.

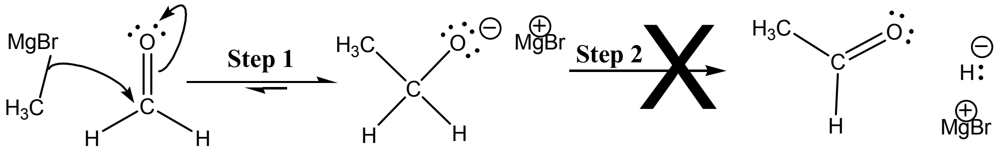
9. Devise a mechanism for the following reaction.



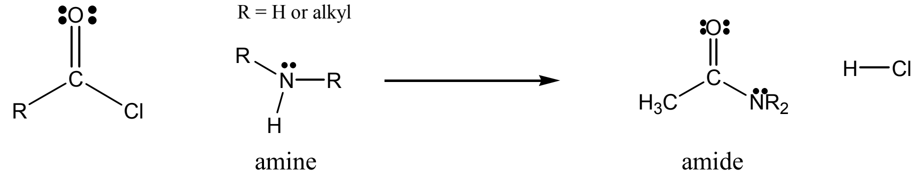
10. Is this reaction uphill or downhill in terms of potential energy? Explain your reasoning.

11. Show the mechanism of a reaction between benzoyl chloride and water (with one equivalent of pyridine, a non-nucleophilic base) to form benzoic acid. Explain why benzoate is not the major product of this reaction.

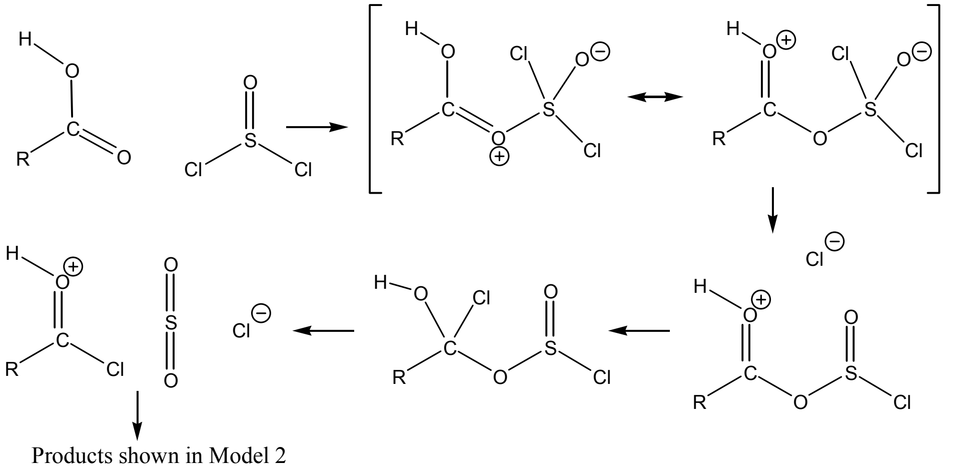
12. Explain why the carbonyl does not reform in the reaction in Model 1. (That is, explain why Step 2 shown below is NOT downhill/favorable from left to right.)



13. Show the mechanism of a reaction between an acid chloride and an amine to form an amide.



14. The mechanism of Synthetic Transformation 23.4 is similar to many you have seen. (Ask your instructor if you will be held responsible for this mechanism.) Each intermediate of the mechanism is drawn below. **Add curved arrows to show electron movement in each step**. (It may be helpful to also draw in lone pairs.)



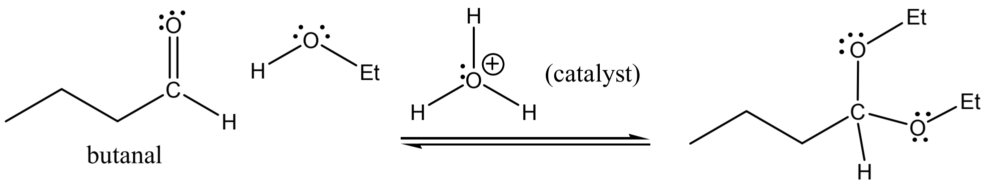
15. Show the mechanism of the reaction between acetyl chloride and excess hydride (H^-), as supplied by a reagent such as $LiAlH_4$, followed by neutralization with dilute acid. (*Hint*: Ethanal is formed during the reaction but is not one of the major final products.)

16. What major product forms when benzoyl chloride is mixed with excess CH_3Li, then neutralized?

17. Read the assigned pages in your text and do the assigned problems.

Exercises for Part B

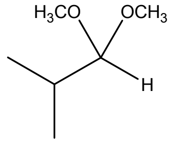
18. Construct a mechanism for the following reaction.



a. Identify the hemiacetal that forms during the reaction above.

b. What could you do to push the above reaction toward a high yield of this acetal?

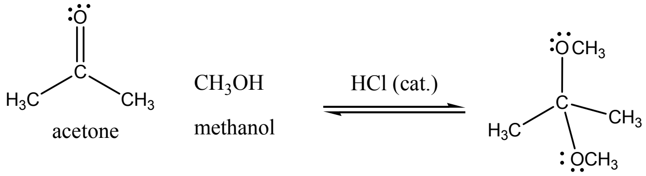
19. Show the mechanism by which the following acetal can be converted into an aldehyde, and draw the resulting aldehyde.



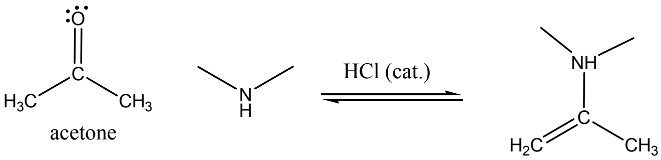
20. Note that some textbooks use the term “acetal” to describe only the product that forms when an alcohol and an acid catalyst are mixed with an aldehyde, and the term “ketal” to describe the product that forms when an alcohol and an acid catalyst are mixed with a ketone. Based on this terminology, draw an example of each of the following: hemiacetal, acetal, hemiketal, ketal.

21. Design a mechanism for each of the following reactions

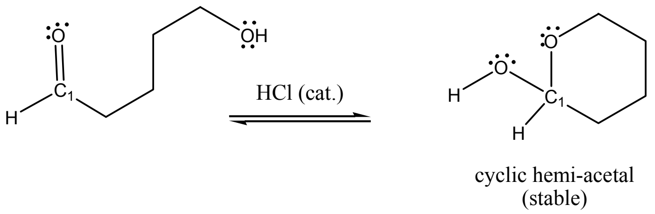
a)



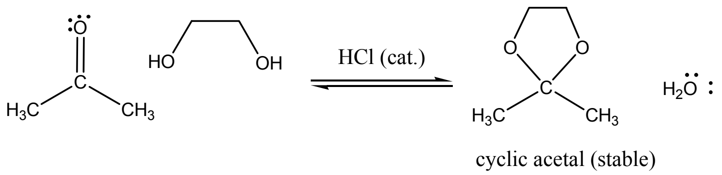
b)



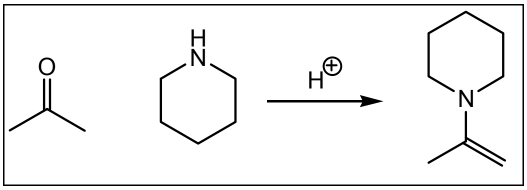
c)

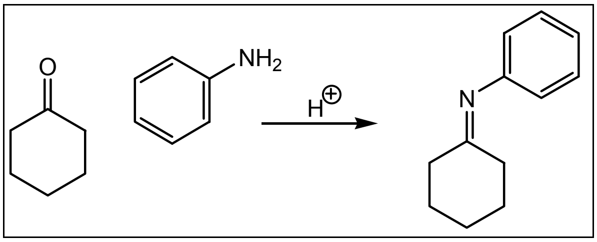


d)



22. Construct a mechanism for each of the following transformations.





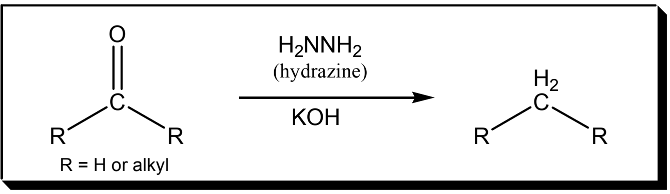
23. What reagents could you add to the imine above to turn it back into the corresponding ketone?

24. The optimal pH for an imine or enamine reaction is 4.5. Construct an explanation for why these reactions do not work at very low pH or at very high pH.

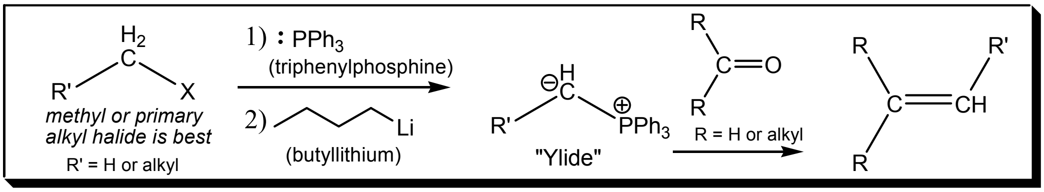
25. When both are possible, an imine formation (C=N bond forms in the last step) is favored over an enamine formation (C=C bond forms in the last step). Explain why reaction with a secondary amine cannot lead to formation of a C=N bond (an imine) in the last step.

Synthetic Transformations 23.12 and 23.13: Wolff-Kishner and Wittig Reactions

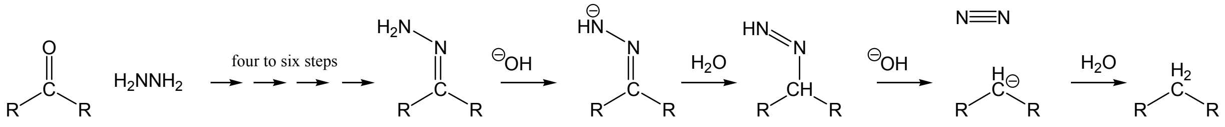
23.12 Wolff-Kishner Reaction

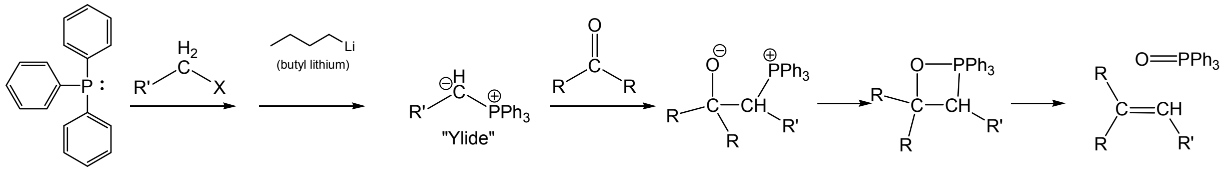


23.13 Wittig Reaction

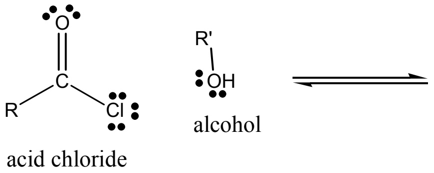


26. The mechanisms of Synthetic Transformations 23.12 and 23.13 involve addition-elimination. They are both very useful in synthesis so you must know them. Knowing their mechanisms will help you remember them. Complete the two mechanisms below by adding curved arrows and missing intermediates (Some key intermediates are shown.).

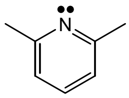




27. Show the most likely products and the mechanism of formation when an acid chloride is mixed with an alcohol.



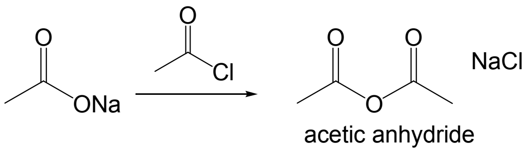
28. Explain why the yield of the reaction in the previous CTQ can be pushed to near 100% with the addition of a non-nucleophilic base such as pyridine or 2,6-dimethylpyridine (shown below).



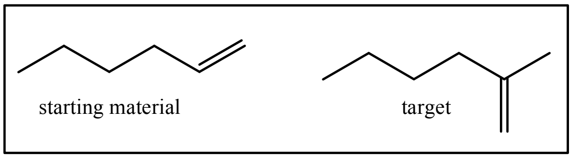
a. Construct an explanation for why 2,6-dimethylpyridine is better than pyridine for this purpose.

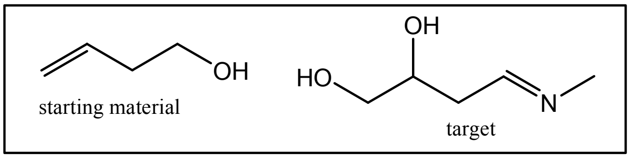
b. What side product would result if a nucleophilic base such as methyl amine were used instead of 2,6-dimethylpyridine?

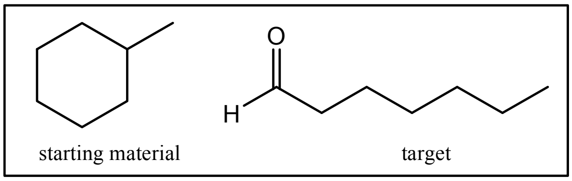
29. In the next ChemActivity we will be studying a class of compounds called acid anhydrides. Devise a mechanism for the reaction at right.

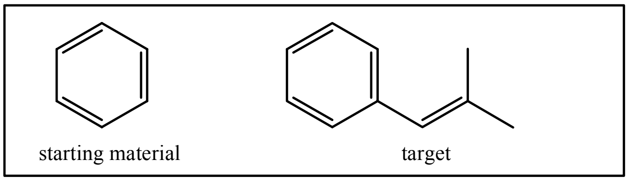


30. Design a synthesis of each target from the starting material given.







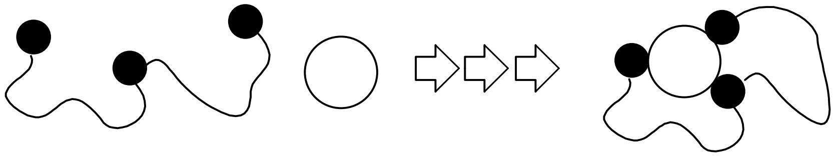


31. Read the assigned pages in your text, and do the assigned problems.

32. Be sure that you have completed Nomenclature Worksheet 4.

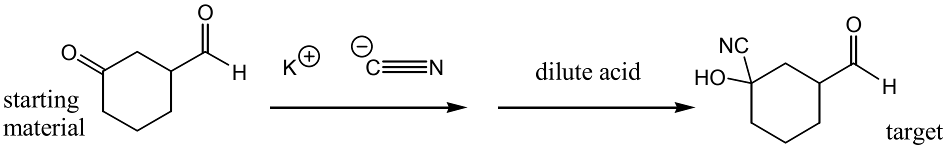
Exercises for Part C

33. Explain why three black balls (see Model 1) tethered together would form a complex that is much more permanent than even the two-ball tethered system.



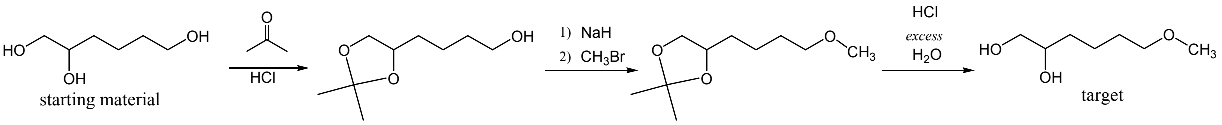
34. Show the mechanism of Synthetic Transformation 23.8.

35. Explain why the following simple synthesis of the target shown will not work.



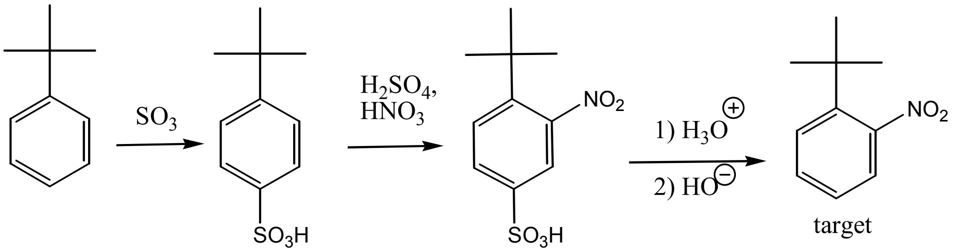
36. Show the mechanism of Synthetic Transformation 23.9: Williamson ether synthesis.

37. Devise a mechanism for the cyclic acetal formation in the first step of the synthesis below.



38. Explain how use of a cyclic acetal protecting group in the previous Exercise is different from other syntheses in this ChemActivity that employ a cyclic acetal protecting group strategy.

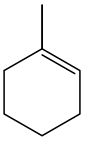
39. Consider the following synthesis.

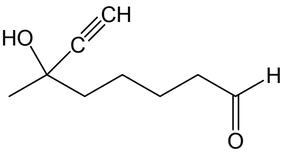


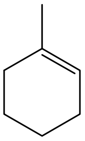
a. Explain why a shorter synthesis consisting of treatment of the starting material with sulfuric acid/nitric acid will not yield the desired target.

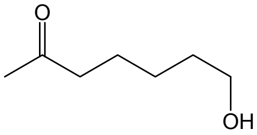
b. Is there a protecting group being used in this synthesis? If so, what is its identity, and what reaction is it preventing?

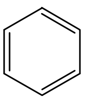
40. Design a synthesis of each target from the starting material given.

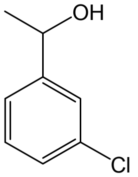
Starting Material 

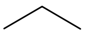
 Target

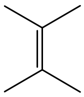
Starting Material 

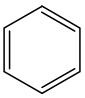
 Target

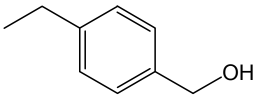
Starting Material 

 Target

Starting Material 

 Target

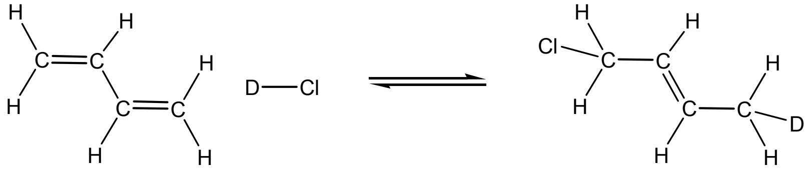
Starting Material 

 Target

41. Read the assigned pages in your text, and do the assigned problems.

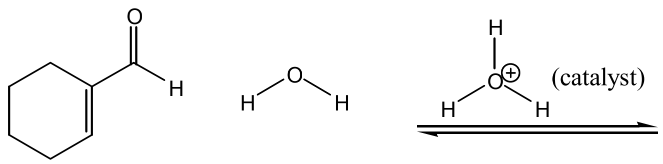
Exercises for Part D

42. Show the mechanism of the following 1,4-addition to a diene. What would a 1,2-addition product of DCl to this diene look like?



43. Construct an explanation for why neither 1,2- nor 1,4-addition to a diene is favorable without an acid catalyst to start the reaction (e.g., using the reagent CH_3ONa followed by dilute acid).

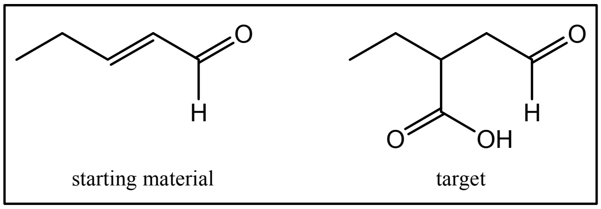
44. Show the mechanism and most likely product that results from 1,4-addition of water to an α,β-unsaturated carbonyl in acidic solution (acid-catalyzed).

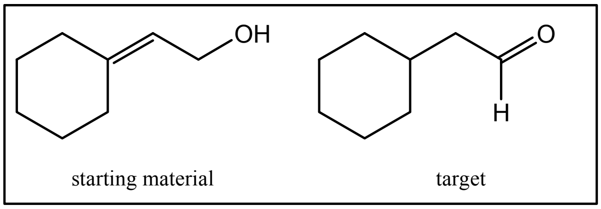


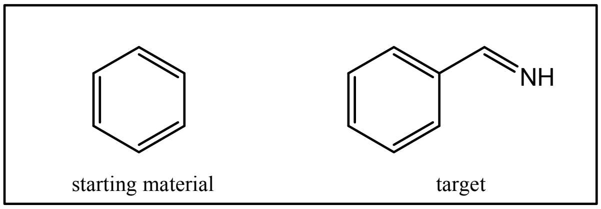
45. Draw the major product(s) that result when the α,β-unsaturated aldehyde in the previous question is exposed to each of the following nucleophiles:
    a. HCN (and a catalytic amount of NaCN)
    b. $LiAlH_4$ followed by neutralization with dilute acid
    c. Pd/C with H_2 gas
    d. Phenylmagnesiumbromide (C_6H_5MgBr) followed by neutralization with dilute acid.
    e. Lithium diphenyl cuprate [$(C_6H_5)_2LiCu$] followed by neutralization with dilute acid.

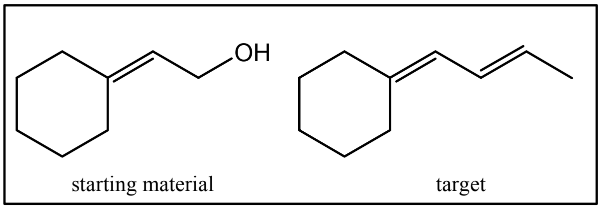
46. For the last two reactions in the previous question, the organometallic reagent is added and allowed to react BEFORE dilute acid is added. Predict what side products would form if these two reagents were added at the same time.

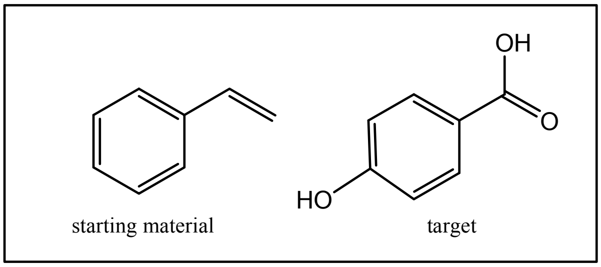
47. Design a synthesis of each target from the starting material given.

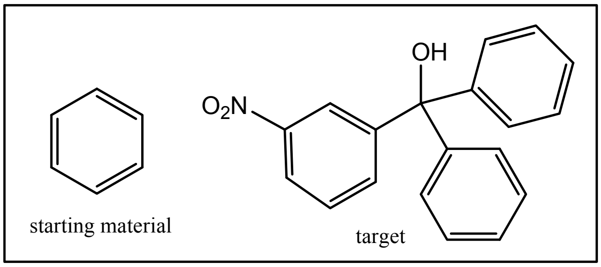












48. Read the assigned pages in your text, and do the assigned problems.

The Big Picture

This ChemActivity is designed to get you comfortable shuffling protons using curved arrows. In preparation for more complex mechanisms in upcoming ChemActivities, you should sit down with a blank piece of paper and make sure you can come up with a reasonable mechanism for imine, enamine, and acetal formation.

Another key objective of this ChemActivity is to refine your understanding of equilibrium and Le Chátelier's Principle. Most of the reactions in this part of the course are not exothermic/downhill, but approximately thermoneutral. Such reactions must be pushed to completion by adding a huge excess of reagents or, even better, by removing an auxiliary product (usually water).

Common Points of Confusion

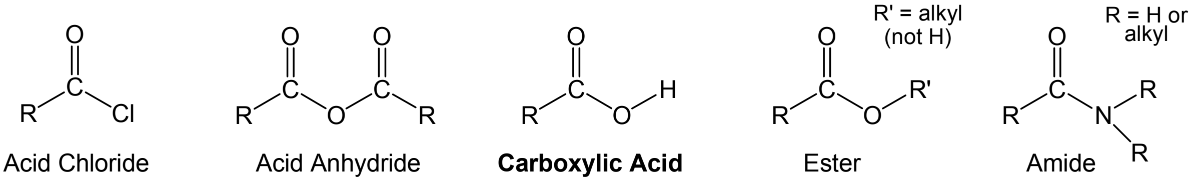
- Students tend to see reactions as either favorable or unfavorable; in this view, either a reaction happens and all reagents are consumed to produce products or no reaction occurs. This is a reasonable way to view a reaction that is either steeply downhill or uphill in terms of energy. Such reactions were featured in the earlier sections of this book. Now we are encountering more and more reactions that are approximately thermoneutral. It does not make sense to think of such reactions as going 100% or 0%. The most likely equilibrium position for a thermoneutral step in a reaction is 50% products and 50% unreacted starting material. Fortunately, such reactions can be "pushed" one way or the other by manipulating other species that are found in the equilibrium expression. Most often this involves adding or removing water.
- The terms reversible and irreversible (See Exercise 3.) should really be replaced with "easily reversed" and "hard to reverse" since the terms reversible and irreversible imply absolutes that are not accurate. Reactions that are steeply downhill from left to right have an equilibrium that strongly favors the products. This means that it is nearly impossible to use Le Chátelier's principle to generate starting material from product. Reactions that are only slightly downhill from left to right are more easily reversed, but such grey area is discounted by the absolute terms reversible and irreversible.
- There are several alternate acceptable mechanisms for **imine**, **enamine**, and **acetal** formation. Different textbooks will show either initial protonation with an acid catalyst or initial reaction of the nucleophile with the carbonyl carbon. The former of these two seems energetically more likely and follows the general rule of thumb that an acid catalyst is usually used in the first step of a mechanism.
- As stated in the previous bullet, imine, enamine, and acetal forming reaction mechanisms are open to debate. Another point in these mechanisms where there is room for argument is in the proton transfers. Usually it is proposed that a solvent or other molecule picks up a proton from one atom and delivers it to another atom (as in Steps 3 and 4 in CTQ 21) but you can also accomplish this via a cyclic transition state. Such **intramolecular proton transfer** steps do not involve any other molecule, and are most favorable for six-member ring transition states. As noted in the activity, four-member cyclic transition states are not favorable.

ChemActivity 24: Carboxylic Acids & Derivatives

PART A: CARBOXYLIC ACIDS, ESTERS, AND AMIDES

(How does the acidic O–H group affect the reaction of a **carboxylic acid** with a nucleophile?)

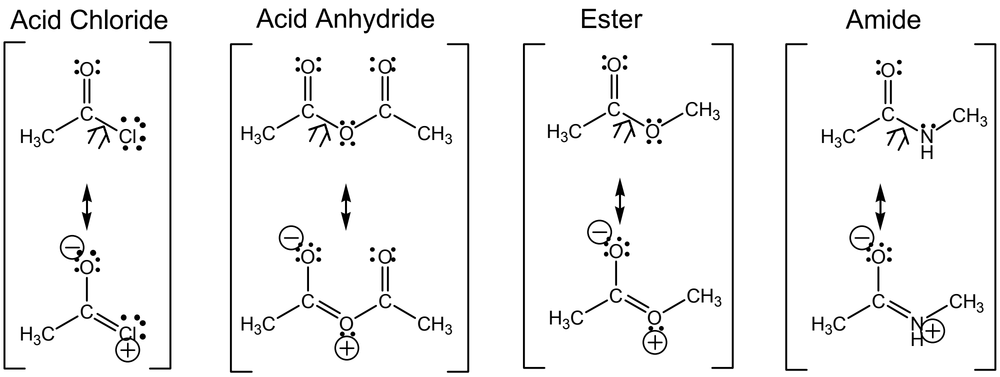
Memorization Task 24.1: Recognize (and Name) Common Carboxylic Acid Derivatives



Nitriles (R-C≡N) are often considered another carboxylic acid derivative because a **nitrile** can be converted easily into a carboxylic acid by addition of acid and water (see Synth. Transformation 11.6.)

Naming rules for carboxylic acids and derivatives are outlined in Nomenclature Worksheet 4.

Model 1: Carbonyl Reactivity



For each compound above we can draw a *second-order* resonance structure to show donation of electron density into the bond marked with =>. This reduces the reactivity of the carbonyl toward a nucleophile.

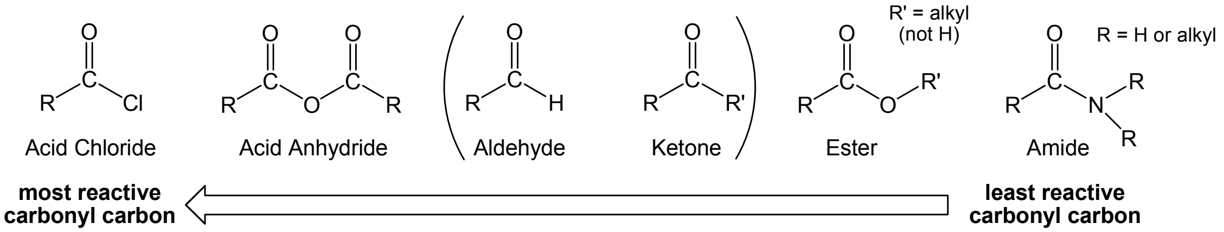
Critical Thinking Questions

1. For each set in Model 1, draw curved arrows showing conversion of the top resonance structure into the *second-order* resonance structure shown below it.

   a. Of the atoms shown donating an electron pair toward the carbonyl carbon, which one donates the **least** electron density? Explain your reasoning. (*Hint*: Consider electronegativity.)

   b. Of the atoms shown donating an electron pair toward the carbonyl carbon, which one donates the **most** electron density? Explain your reasoning. (*Hint*: Consider electronegativity.)

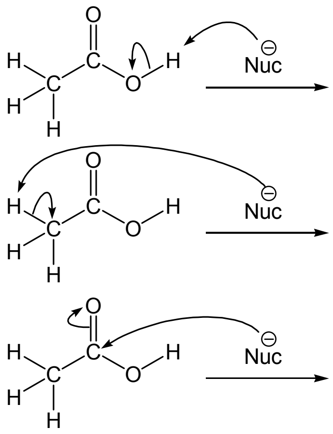
Memorization Task 24.2: Relative Carbonyl Reactivity (with a Nucleophile)



Note that aldehydes and ketones are not carboxylic acid derivatives so it can be hard to make a direct comparison. Additionally, very large R groups can reduce the reactivity of a carbonyl due to increased steric repulsion of the nucleophile.

2. (Check your work.) Are your answers to CTQ 1 consistent with Memorization Task 24.2? Explain.

Model 2: Acid-Base Reactivity of a Carboxylic Acid (CA)



Critical Thinking Questions

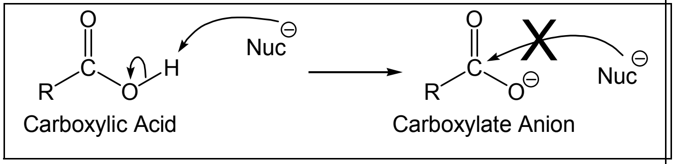
3. Model 2 shows three possible ways that a nucleophile that is also a base (represented as Nuc $^{\ominus}$) could react with acetic acid. Predict which one of these pathways is favored over the other two.
   a. Draw the product(s) of each set of curved arrows. (Include all important resonance structures.)
   b. Label each set of curved arrows with the appropriate reaction type. Choose from: **Acid-Base, Elimination, Electrophilic Addition,** or **Nucleophilic Addition**.

4. (Check your work.) Two of the three reactions depicted in Model 2 are acid-base reactions. Each of these acid-base reactions results in a conjugate base with two important resonance structures.
   a. Check that you drew both important resonance structures for each conjugate base.
   b. Circle the conjugate base that is lower in potential energy, and explain your reasoning. (Label this reaction in Model 2 “**favored reaction pathway.**”)

5. (Check your work.) Is your answer in part b of CTQ 4 consistent with Memorization Task 24.3?

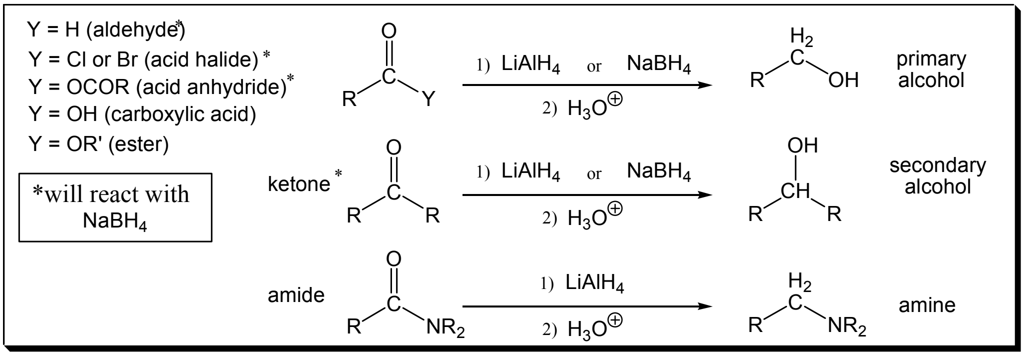
Memorization Task 24.3: Carboxylic Acids Donate an H^+ (except in acidic conditions)

A nucleophile that is also a base **will remove the acidic H from a carboxylic acid rather than bond to the carbonyl carbon**.



Once this H is removed, the anionic carboxylate will repel almost all nucleophiles. Notable exceptions are hydride (as supplied by $LiAlH_4$ – see Synth. Transf. 24.1) and lithium reagents.

Synthetic Transformation 24.1: Carboxylic Acid Derivatives—Reduction with Hydride

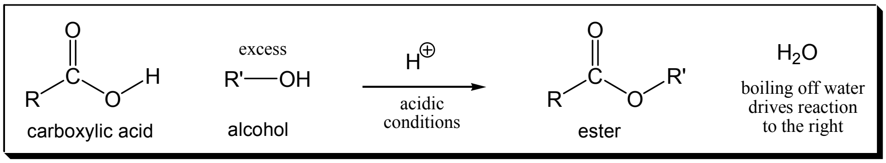


6. List functional groups that require use of the more powerful $LiAlH_4$ to accomplish a reduction.

Model 3: Nucleophilic Addition to a Carboxylic Acid (at low pH)

In acidic conditions (low pH) the O—H bond of a carboxylic acid stays intact. This allows nucleophilic addition to the carbonyl carbon by an alcohol to form an **ester**, as shown in Synth. Transf. 24.2.

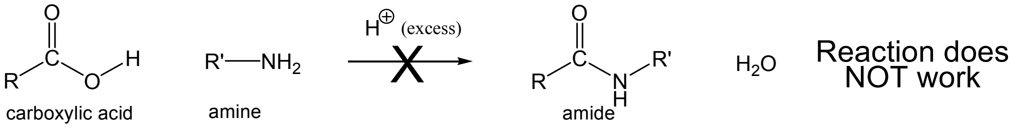
Synthetic Transformation 24.2: Acid-Catalyzed Ester Synthesis



Critical Thinking Questions

7. Devise a mechanism for Synthetic Transformation 24.2. *Hint*: The first step is protonation of the carbonyl oxygen by the acid catalyst.

8. Construct an explanation for why the following amide-forming reaction analogous to the ester-forming reaction shown in Synthetic Transformation 24.2 does NOT produce the desired product. (*Hint*: Consider what species in solution is most likely to react with the acid catalyst.)



Memorization Task 24.4: Few Nucleophiles React Directly with the Carbonyl of a CA.

Alcohols are among the only nucleophiles that can undergo nucleophilic addition to the carbonyl of a **carboxylic acid**. Other, more basic nucleophiles fail because of one of the following reasons…

(1) *(Under basic conditions—with excess basic nucleophile)* The nucleophile removes the acidic H from the carboxylic acid, rendering its carbonyl virtually unreactive.

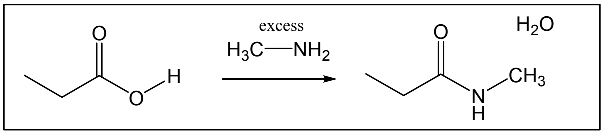
(2) (*Under acidic conditions—with excess acid*) A nucleophile that is also a good base will be protonated by the acid catalyst and consequently become non-nucleophilic

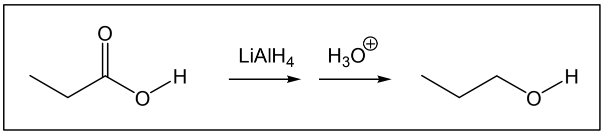
9. (Check your work.) Which reason in Memorization Task 24.4 best explains the failure of the reaction at the top of the page?

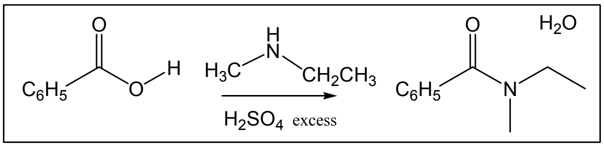
10. Only three of the following reactions produce a significant yield of the product shown.

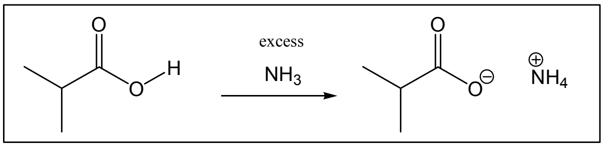
a. Cross out the reaction arrows of the other three reactions—the ones expected to fail.

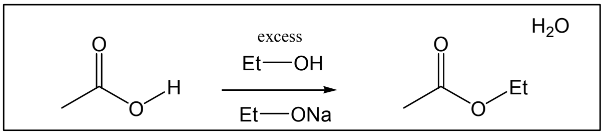
b. Put a (1) or (2) next to each failed reaction to indicate which reason in Memorization Task 24.4 best explains why that reaction is doomed to failure. (Any species in *excess* is labeled.)

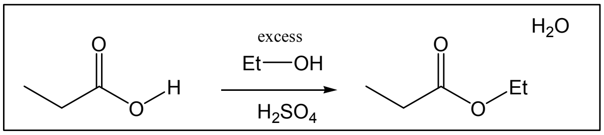












***If your group finishes early, begin working on the extensive homework* Exercises for Part A**. *These contain a number of important synthetic transformations that build on the work you have just completed.*

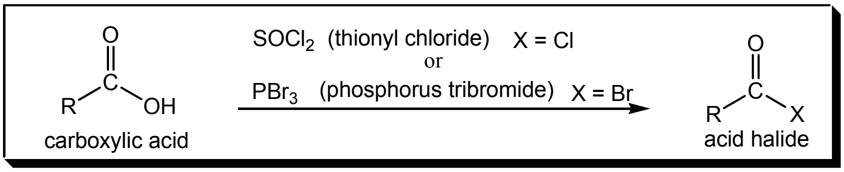
PART B: ACID HALIDES AND ACID ANHYDRIDES

(Is there a way to make an amide from a carboxylic acid?)

Model 4: Acid Halides (Alkanoyl Halides)

In Part A of this activity we discovered that the OH group of a carboxylic acid makes it impossible to transform it directly into an amide. This problem and many others can be solved by replacing the OH group with a halogen via Synthetic Transformation 23.4.

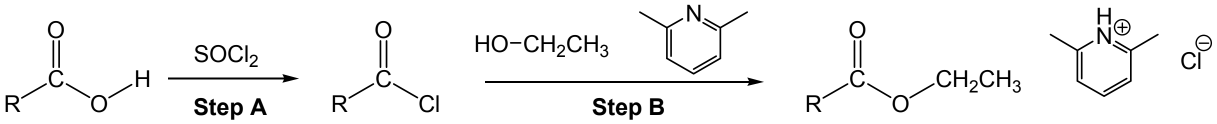
Synthetic Transformation 23.4: Preparation of Acid Halides from Carboxylic Acids


carboxylic acid
$SOCl_2$ (thionyl chloride) X = Cl
or
PBr_3 (phosphorus tribromide) X = Br
acid halide

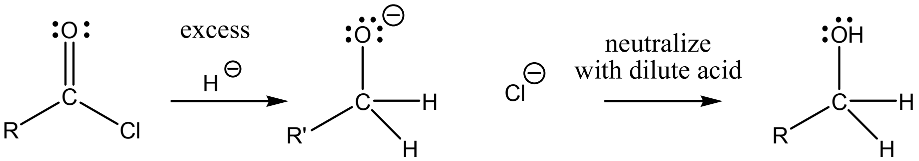
Critical Thinking Questions

11. Based on Model 1 at the start of this ChemActivity, which carbonyl is more reactive, that of a carboxylic acid or that of an acid halide?

12. Use curved arrows to show the mechanism of Step B of the following synthesis. **Recall that S_N1 and S_N2 reactions cannot take place at *sp*^{2}-hybridized carbons.**



13. When excess hydride (e.g., $NaBH_4$ or $LiAlH_4$), lithium reagent (R-Li), or Grignard (R-MgBr) is added to an acid halide, **two molar equivalents** of nucleophile are incorporated into the product. Devise a mechanism for this reaction, assuming the nucleophile is hydride anion (H^-).



Model 5: Acid Halides with LiR_2Cu Reagents

A **lithium dialkyl cuprate (LiR2Cu) reagent** will…

- NOT react with an aldehyde or ketone,
- *but will* react with the activated carbonyl of an acid halide.

Critical Thinking Questions

14. (E) Which is more reactive?

the carbonyl of an aldehyde/ketone
or
the carbonyl of an acid halide
(circle one)

15. (Check your work.) Explain how information in Model 5 supports your answer to the previous question.

16. Draw the major product of each reaction on this page →

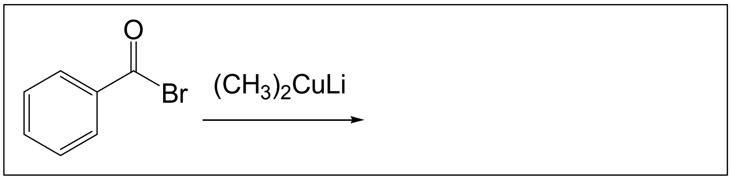
Write "**no reaction**" if you do not expect a reaction.

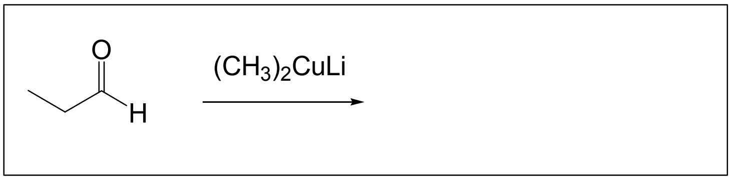
Assume…

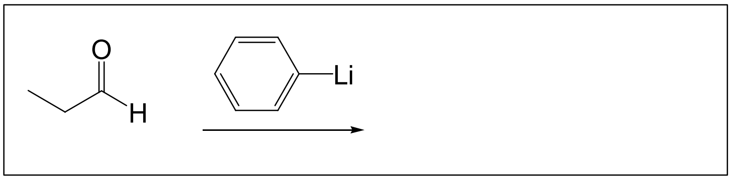
- nucleophile is present in excess (except where noted)

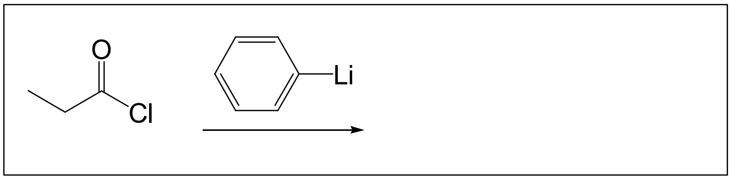
and that…

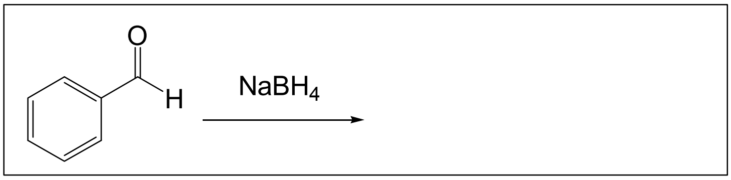
- if necessary, the product mixture is neutralized at the end of each reaction.

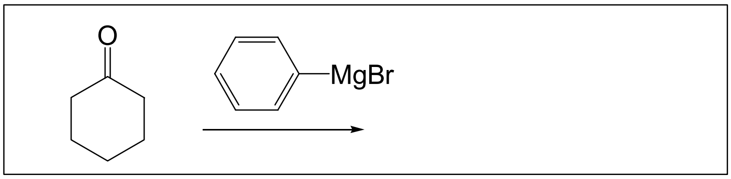


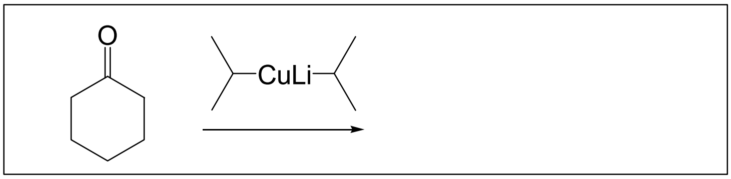


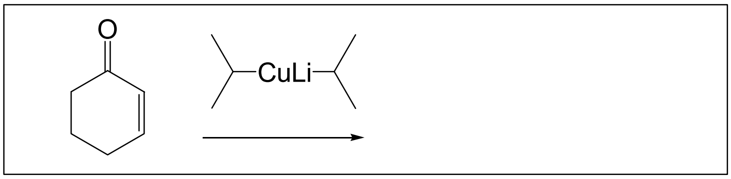


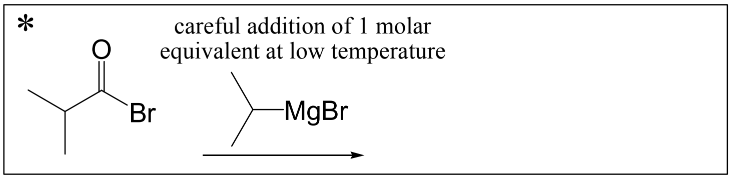












careful addition of 1 molar equivalent at low temperature

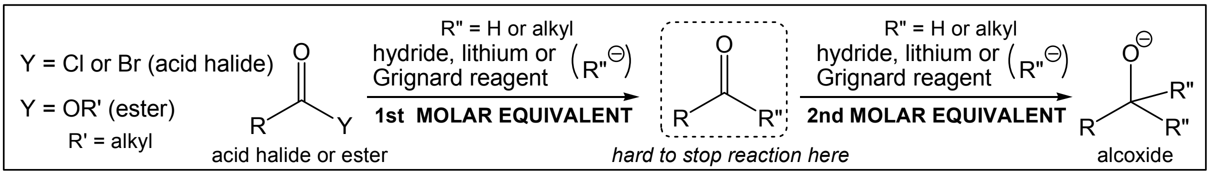
* *This reaction is hard to control and will result in some alcohol side product.*

Mem. Task 24.5: Esters are less reactive than acid halides in reactions with nucleophiles

Esters will react with $LiAlH_4$, lithium reagents (R-Li), and Grignard reagents (R-MgBr), but not $NaBH_4$ or lithium dialkyl cuprate reagents (LiR_2Cu).

Memorization Task 24.6: Acid halides and esters consume two equivalents of H^- or C^-

When $LiAlH_4$, a lithium reagent (R-Li), or a Grignard (R-MgBr) is added to an **acid halide** or **ester** it is nearly impossible to stop the reaction at the aldehyde/ketone (*see dotted box*).



For this reason, excess nucleophile is almost always used. This gives a high yield of the fully reduced alkoxide product instead of a mixture of alkoxide, aldehyde/ketone, and unreacted starting material.

Unless otherwise noted, assume excess nucleophile is present in these reactions.

To stop at the aldehyde a special reducing agent (such as DIBAH) may be used. To stop at the ketone a lithium dialkyl cuprate reagent may be used. These reactions are summarized at the end of this activity.

17. Draw the major product/s of each reaction at right →

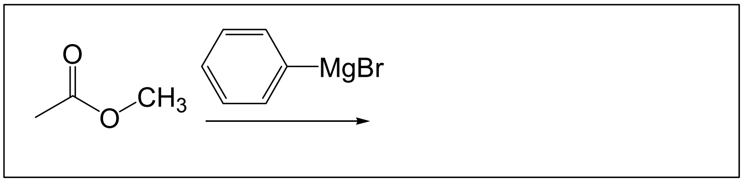
Write "**no reaction**" if you do not expect a reaction.

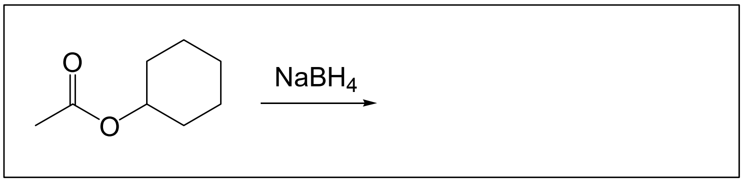
Assume…

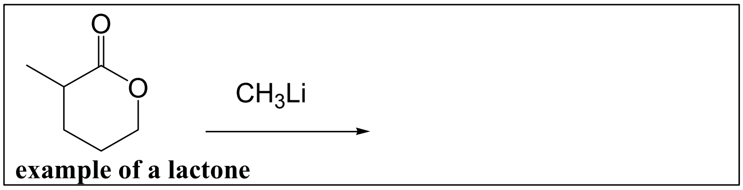
- nucleophile is present in excess

and that...

- if necessary, the product mixture is neutralized at the end of each reaction.







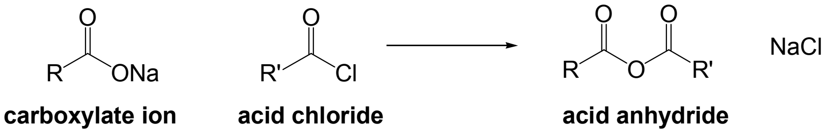
18. (Check your work.) The products of the first reaction above are 1,1-diphenylethanol + methanol. The second reaction yields no products. However, *if* $LiAlH_4$ is used in place of $NaBH_4$ it produces ethanol + cyclohexanol. Show the mechanism of this second reaction with $LiAlH_4$, assuming the nucleophile is hydride anion (H^-).

19. (Check your work.) A cyclic ester is called a **lactone**. The reaction of the lactone in the third reaction on the previous page yields **4,5-dimethylhexane-1,5-diol**. Draw this product, check your work above, and devise a mechanism for this reaction (assuming the nucleophile is a H_3C^- anion).

Model 6: Acid Anhydrides

Think of an acid anhydride as a less-reactive replacement for an acid halide. Acid anhydrides are often used in place of acid halides when a slower, more controlled reaction is necessary.

The name ***acid anhydride*** *refers to the fact that you can generate a symmetrical acid anhydride by heating a pure sample of the corresponding carboxylic acid while removing the water that is produced ("anhydride" means "without water"). An easier way to generate an acid anhydride is to mix an acid halide with a carboxylate anion, as shown below.*

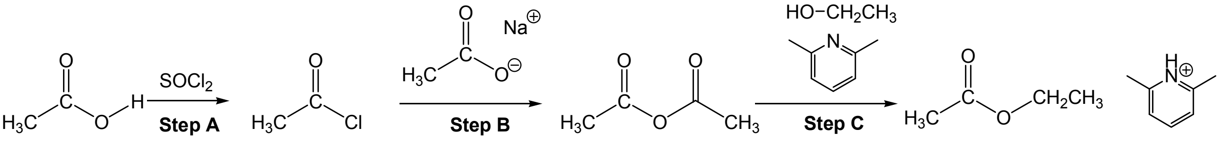


Critical Thinking Questions

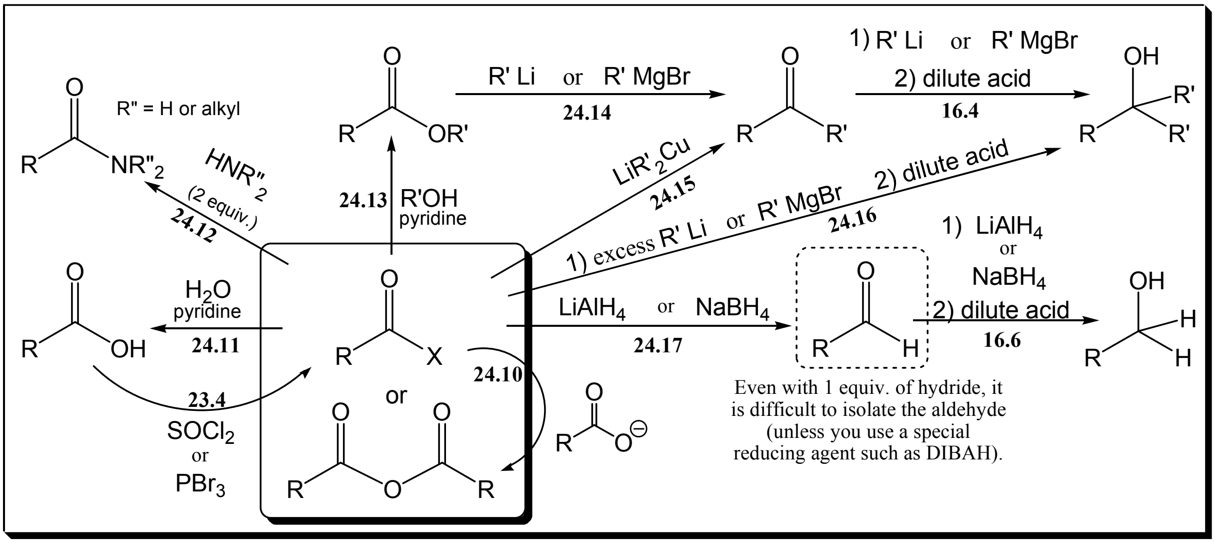
20. (E) According to Models 1 and 6, which is more reactive, the **carbonyl of an acid halide** or **the carbonyl of an acid anhydride?** (circle one).

21. Devise a mechanism for the reaction in Model 6.

22. The ester synthesis at the beginning of this activity can be accomplished via an acid anhydride as shown below. Show the mechanism of **Step C** in this synthesis. (Another product is formed in this reaction, but not shown below. What is it?)



Synthetic Transformations 24.10-24.17: Acid Halides and Anhydrides—Reactions

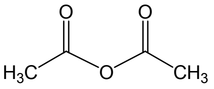


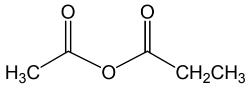
Critical Thinking Questions

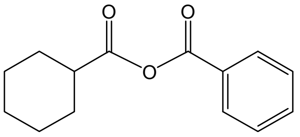
23. Label the structures in the Synthetic Transformations above according to their functional group category. Choose from **alcohol** (specify 1°, 2°, or 3° if indicated)**, amine, aldehyde, ketone, amide, ester, carboxylic acid, carboxylate, acid halide,** or **acid anhydride**.

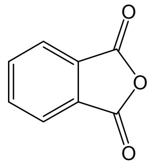
24. The acid anhydride shown in Model 6 has an R group on one end and an R' group on the other end. When R = R' this it is called a **symmetrical acid anhydride**. (These are most common.) When R and R' are different it is called an **asymmetrical acid anhydride**.

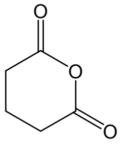
    a. (E) Identify each acid anhydride below as symmetrical or asymmetrical.





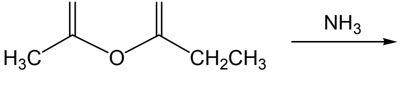






    b. Construct an explanation for why use of an asymmetrical acid anhydride usually gives rise to two different products.

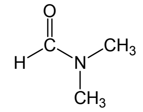
    c. Draw both amide products that arise if the asymmetrical acid anhydride below is treated with excess ammonia (NH_3).



Exercises for Part A

1. Which compound in Model 1 has the most double-bond character in the bond marked in the top structure with an arrow =>? Explain your reasoning.

2. Construct an explanation for why a carbon NMR spectrum of *N,N*-dimethylformamide obtained at room temperature shows three peaks at 161 ppm, 36 ppm and 32 ppm.

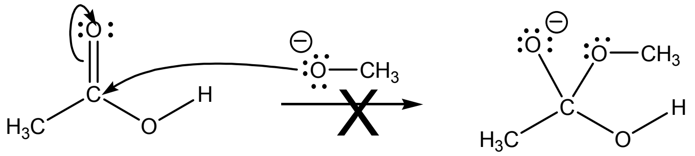


3. Is your explanation in the previous question consistent with the finding that a carbon NMR spectrum of *N,N*-dimethylformamide obtained at an elevated temperature shows only two peaks: one at 161 ppm and the other at 34 ppm? Explain.

4. Label the O—H bond-breaking arrow in Model 2 with a "+5" to indicate that it takes approximately +5 pK_a units of energy to break this bond and liberate an H.

5. Label the C—H bond-breaking arrow in Model 2 with a "+20" to indicate that it takes approximately +20 pK_a units of energy to break this bond and liberate the H on the carbon *alpha* (α) to the carbonyl. *Recall that normal C—H bonds take up to 50 pK_a units of energy to break. Resonance stabilization makes C_α–H_α bonds much easier to break. The resulting chemistry is the subject of the next three ChemActivities.*

6. Methoxide ion ($^-OCH_3$) is an excellent nucleophile, yet the following addition does not occur.



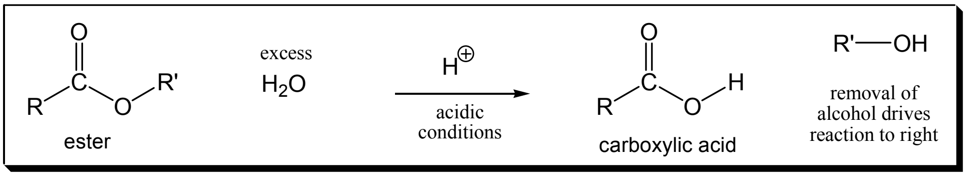
Reaction
Does Not
Occur

   a. Draw the reaction and resulting products that are likely to form instead of the one shown.

   b. Construct an explanation for why the **conjugate base of acetic acid** is formed preferentially over the **nucleophilic addition product above**

7. Synthetic Transformation 24.2 is reversible. Describe a laboratory procedure that would allow you to reverse this reaction and generate a carboxylic acid from an ester as shown in Synthetic Transformation 24.3, below.

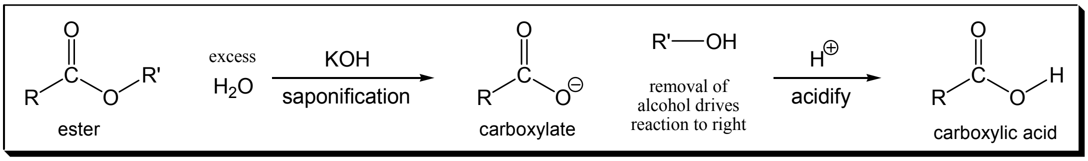
Synthetic Transformation 24.3: Acid-Catalyzed Ester Hydrolysis



8. Show the mechanism of Synthetic Transformation 24.3.

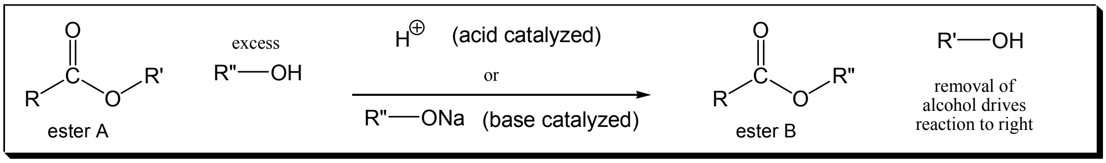
9. An attempt to generate a carboxylic acid from an ester under basic conditions leads to a carboxylate, as shown in Synthetic Transformation 24.4 below. (Note that the carboxylate can be easily protonated in a second step to give the desired carboxylic acid.) This reaction is called **saponification** for the *Latin* word for soap (*saponis)* because this reaction is used in the making of soap from fats (which are long-chain esters). Show the mechanism of this transformation.

Synthetic Transformation 24.4: Ester Saponification (Base-Catalyzed CA Synthesis)



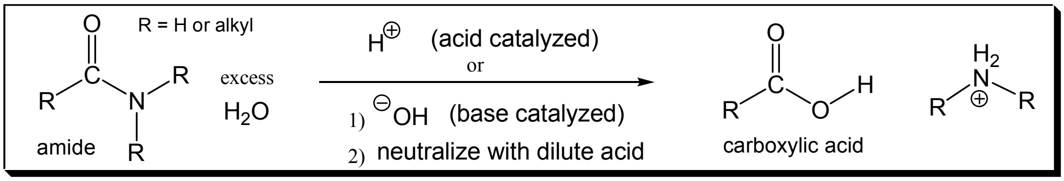
10. Trans-esterification (the conversion of one ester into a different ester) can be accomplished using reaction conditions analogous to either Synth. Transf. 24.3 (acidic conditions) or Synth. Transf. 24.4 (basic conditions). Show the mechanisms of both acid- and base-catalyzed trans-esterification.

Synthetic Transformation 24.5: Trans-Esterification

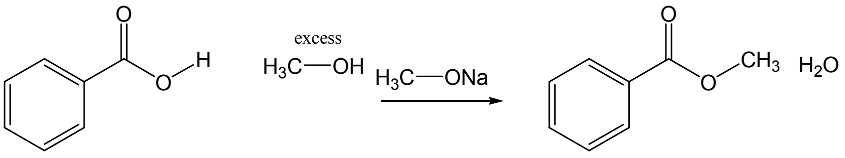


11. Hydrolysis of an amide is similar to trans-esterification. Show the mechanisms of both acid- and base-catalyzed amide hydrolysis.

Synthetic Transformation 24.6: Acid- or Base-Catalyzed Amide Hydrolysis



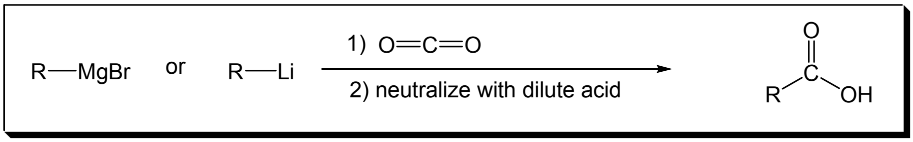
12. Conversion of a carboxylic acid to an ester does NOT work in basic conditions, and the product in the box below does not form. Use curved arrows to show the mechanism and product of the side reaction that would result if this reaction were attempted in basic conditions.



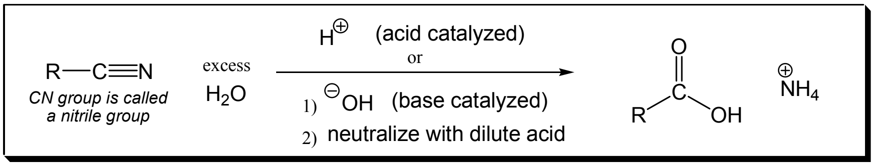
13. The reaction in the previous question does not work in basic conditions. Explain how it is different from Synthetic Transformations 24.4 through 24.6, which do work in basic conditions.

14. Synthetic Transformations 24.7 and 11.6 are both common ways of preparing a carboxylic acid. Use curved arrows to show the mechanism of each reaction.

Synthetic Transformation 24.7: 1° Grignard or Lithium Reagent with Carbon Dioxide

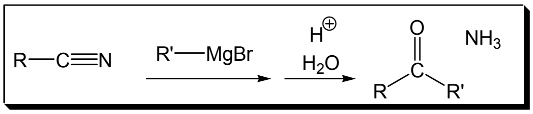


Synthetic Transformation 11.6: Nitrile Hydrolysis



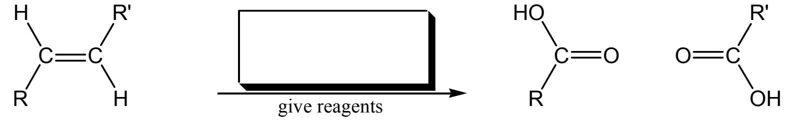
15. The C≡N bond of a nitrile is analogous to the C=O bond of a carbonyl compound. Given this, devise a mechanism for the reaction at right. (*Hint*: An imine is one of the intermediates.)

Synth. Transf. 24.8: Grignard + Nitrile

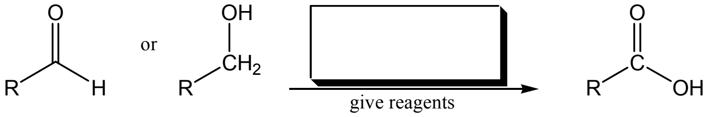


16. (*Review*) Write appropriate reagents in the boxes over each reaction arrow.

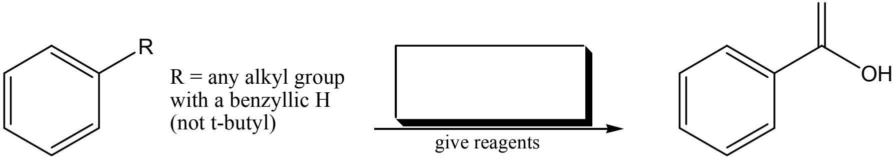
see
**Synth. Transf.
10.11**



see
**Synth. Transf.
10.8**

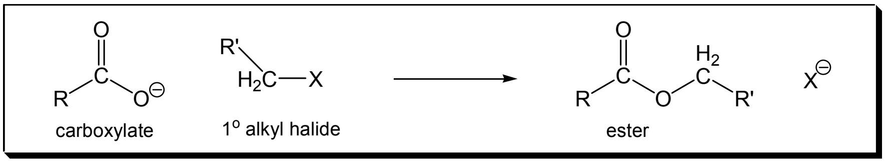


see
**Synth. Transf.
22.3**



17. Devise a one-step mechanism for the following reaction. (What type of mechanism is this?)

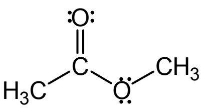
Synthetic Transformation 24.9: Formation of an Ester from a 1° Alkyl Halide

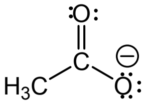


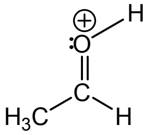
18. Read the assigned pages in your text, and do the assigned problems.

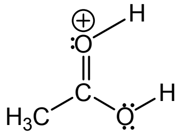
Exercises for Part B

19. Rank the following compounds from…“1 = best electrophile” to “4 = worst electrophile,” and explain your reasoning.

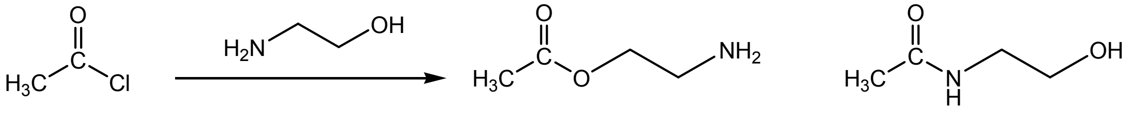


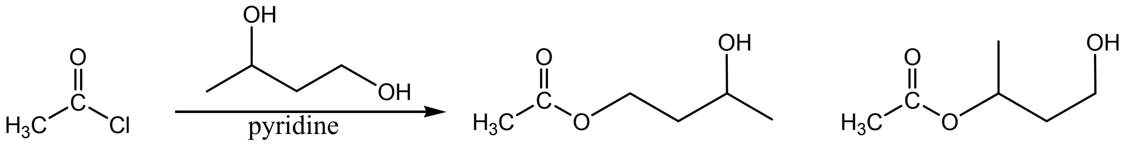






20. For each reaction, state which product is more likely, and explain your reasoning.

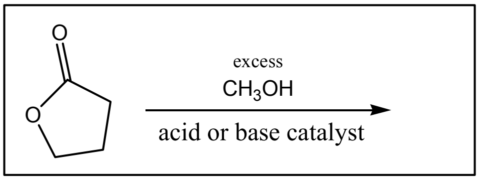


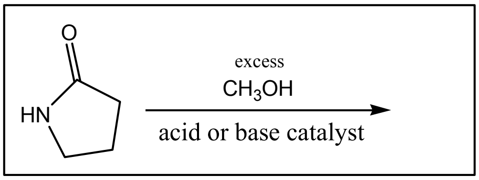


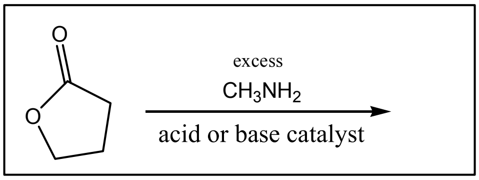
21. Construct an explanation for why the last reaction in CTQ 16 can be controlled enough to give a reasonable yield of ketone, while an analogous reaction using a smaller nucleophile (such as a methyl group [CH_3MgBr]) cannot be controlled.

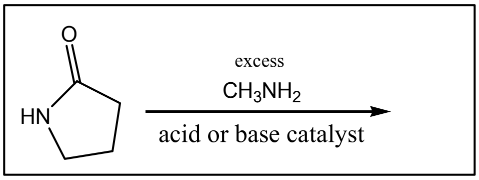
22. Construct an explanation for why two molar equivalents of amine are needed to obtain a high yield of amide from an acid halide or acid anhydride.

23. Draw the major product, and show the mechanism of each of the following reactions with an acid catalyst and then with an appropriate base catalyst. (Draw the structure of the best base catalyst for each reaction.)



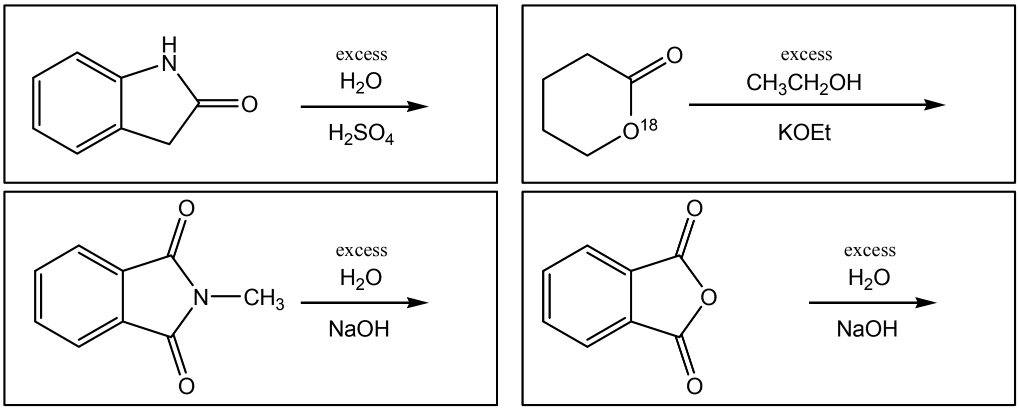




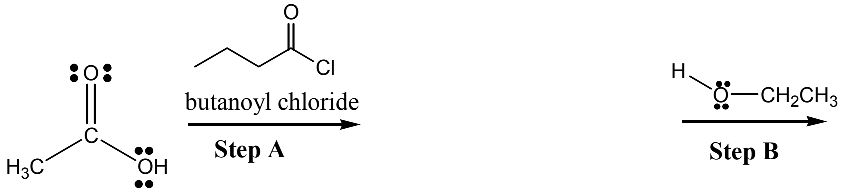


lactone (cyclic ester) **lactam (cyclic amide)**

24. Try to draw the most likely product of each of the following reactions, then check your work by drawing the mechanism of the reaction. *Tip: These types of questions can be very difficult to answer correctly without sketching the mechanism.*



25. Complete the synthesis of the asymmetrical anhydride, and draw all four organic products that result (two esters and two carboxylic acids).

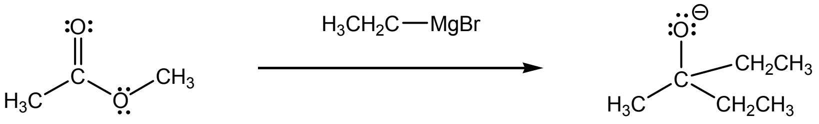


26. Acid halides and acid anhydrides allow convenient synthesis of carboxylic acid derivatives because they each have a good leaving group attached to the carbonyl carbon.

a. What is this leaving group in the case of an acid halide?

b. What is this leaving group in the case of an acid anhydride? (*Hint*: The leaving group is not just a single atom.)

c. If you use a nucleophile that is strong enough, you don't need a good leaving group. A Grignard reagent is an example of such a nucleophile. In the following synthesis of an alkoxide. Show the mechanism of the reaction, assuming the nucleophile is $CH_3CH_2^-$. (Remember that OH or OR are good leaving groups ONLY in strongly basic conditions, such as in a Grignard or Lithium reaction.)

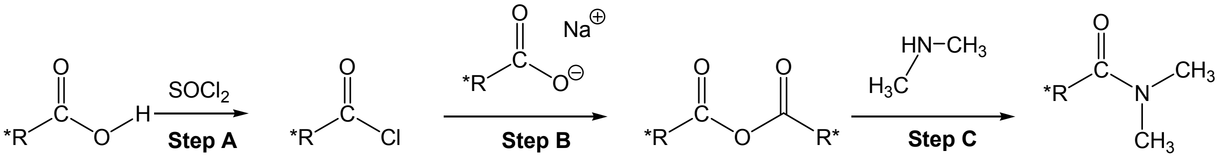


27. Repeat part c of the previous question using $LiAlH_4$ in place of ethyl magnesium bromide.

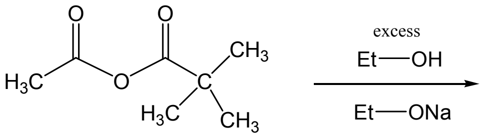
Note that organometallic reagents (lithium reagents, Grignard reagents, $LiAlH_4$, etc.) often have a mechanisms of action that involve the metal atom and are more complicated than if the nucleophile were truly a carbanion or a hydride with a simple counterion. For our purposes the correct product and a reasonable answer can be found by assuming these reagents work as if they were a carbanion or a hydride with a simple counterion.

28. Starting from any carboxylic acid(s), devise a synthesis of the 1st three acid anhydrides in CTQ 24a.

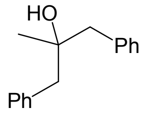
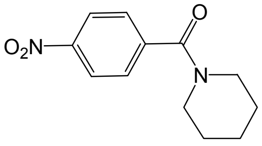
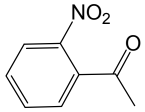
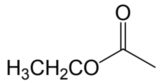
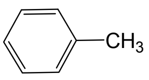
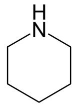
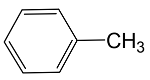
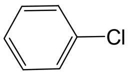
29. The R* on the molecules below represents a chiral R group. Assume that the carboxylic acid starting material is very costly because of this chiral group. Construct an explanation for why, in this case, it would be a poor choice to use an acid anhydride to transform this acid into a derivative (e.g., the dimethyl amide shown). *Hint*: Draw the other organic product produced in Step C.



30. Construct an explanation for why the following asymmetrical anhydride gives a much higher yield of ethyl acetate than ethyl 2,2-dimethylpropionate.



31. Design an efficient synthesis of each of the following target molecules. All carbon atoms must come from the starting material(s) given.

Target			
Starting material	 	 	 $HC \equiv CH$

32. Read the assigned pages in your text, and do the assigned problems.

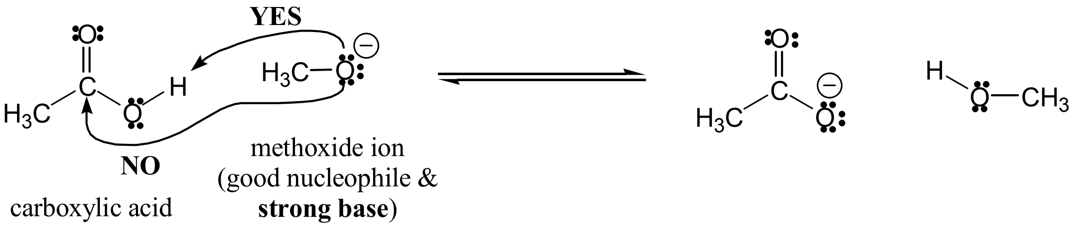
The Big Picture

In principle, carboxylic acids, esters, and amides can be interconverted by manipulating Le Cháelier’s principle (as long as you avoid the complications caused by deprotonation of a carboxylic acid). Not all of these transformations are presented as official Synthetic Transformations because some are not often used in synthesis. For example, you can change an ester into an amide by treating it with excess amine and catalyst, and you can even do the opposite with sufficient time and heat. However, in practice it often makes sense in terms of time and overall yield to accomplish most carboxylic-acid-derivative syntheses by first making an activated carbonyl compound, either an acid halide or acid anhydride.

Common Points of Confusion

- It seems so simple, but many students forget that carboxylic acids are acidic! This gives rise to the following problems and resolutions…

  Nucleophilic addition to a **carboxylic acid** carbonyl group is impossible when the nucleophile is also a good base. (Nuc^- acts as a base and removes the acidic H^+ instead.)



  To solve this problem we must use a nucleophile that is a very weak base. For example, use methanol ($HOCH_3$) instead of methoxide ion ($^-OCH_3$).

  However, since methanol is a weak nucleophile, we must activate the carbonyl with an **acid catalyst to make the carbonyl carbon a better electrophile.**

- Remember that hydroysis of an ester or amide in basic conditions leads to a **carboxylate** (not a carboxylic acid).

- Students often forget that use of excess $LiAlH_4$, lithium, or Grignard reagent with an acid halide, acid anhydride or ester will result in incorporation of two molar equivalents of nucleophile in the product; whereas lithium dialkyl cuprates will deliver only one equivalent (except to esters). This is a consequence of the fact that lithium dialkyl cuprates do NOT react with aldehydes, ketones, or esters.

- Reduction of an **ester** (RCO_2R') with a **hydride** reagent (e.g., $LiAlH_4$) leads to an alcohol (ROH), not an ether (ROR') as some students assume. The source of this misconception appears to be the fact that reduction of a carboxylic acid or amide with this same reagent appears to imply that the reagent turns a C=O into a CH_2. The mechanism of the ester reduction reveals that the OR group is lost as a leaving group. (This is one of the rare instances of RO^- functioning as a leaving group). The carbonyl oxygen remains and becomes the alcohol oxygen of the product. See CTQ 17.

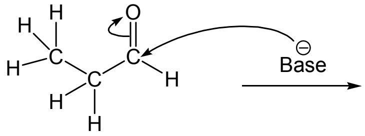
- Synthetic transformations on test and quizzes often do not specify how much of a particular reagent is added. In such situations you are to assume that the appropriate amount is added. That is, if the reagent is a catalyst that is required only in trace amounts, then assume there is a trace amount (even if it doesn't say "trace amount" next to the reagent). Conversely, if excess reagent is necessary to effect a reasonable reaction it may not say "excess" next to the reagent, but you are to assume excess reagent is present. The exception to this rule is when 1 equivalent of a reagent gives a very different product than multiple equivalents. In such instances (such as the addition of 1 molar equivalent of a bulky Grignard to an ester at low temperature) the number of molar equivalents of reagent will likely be specified.

- Ring opening of lactones (cyclic ester) and **lactams** (cyclic amides) really belongs in the previous activity (but there were already too many long mechanisms there, so they are presented here). The key error that students make in answering questions (especially multiple-choice questions) is to assume that the ring oxygen of a **lactone** remains attached to the carbonyl carbon in a resulting ester or carboxylic acid. This misconception is often tested using an O^{18}-labeled oxygen as in Exercise 24. The best way to answer such questions is to quickly sketch the mechanism of the reaction.

ChemActivity 25: Enolate and Enol Nucleophiles

(How can an aldehyde or ketone act as a nucleophile?)

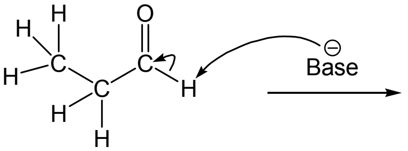
Model 1: Acid-Base Reactivity of Aldehydes

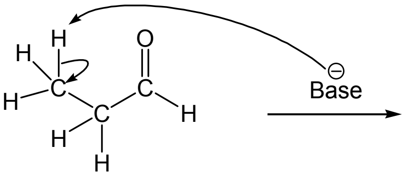


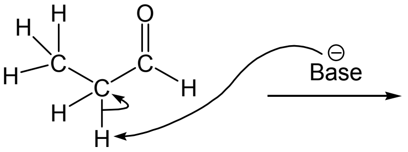
Many nucleophiles are also good bases (e.g., RO^{-}, R_2N^{-}, R_3C^{-}, H^{-})

In the past two ChemActivities we have focused on reactions such as the one at right, in which a basic species acts as a nucleophile, making a bond to a carbonyl carbon.

Such a species can also act as a base. Shown below are three possible acid-base reactions of this pair.







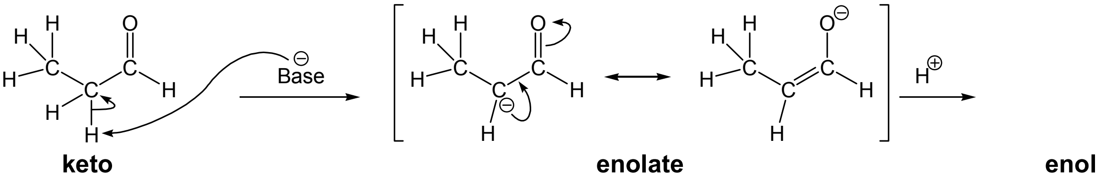
Critical Thinking Questions

1. Draw the product of each set of curved arrows. (Include all important resonance structures.)
2. Only one of these three acid-base reactions is favorable. Which one? Explain your reasoning.

3. (Check your work.) Is your answer above consistent with Memorization Task 25.1?

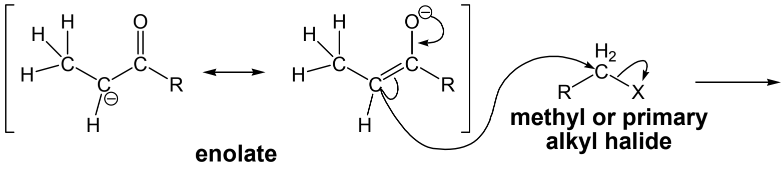
Memorization Task 25.1: Enolate Ions

The most acidic H on a carbonyl compound (except a carboxylic acid) is the **alpha hydrogen**. Removal of an H_α gives a resonance-stabilized **enolate ion** that acts as a versatile carbon nucleophile.



4. (E) Draw the structure of the enol that is missing from Memorization Task 25.1.

Model 2: Enolate as Nucleophile

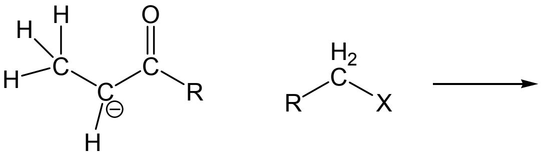


Critical Thinking Questions

5. Either resonance form of an enolate can be shown making a bond to an electrophile. A very useful application of this, an enolate in reaction with a methyl or primary alkyl halide, is shown above.

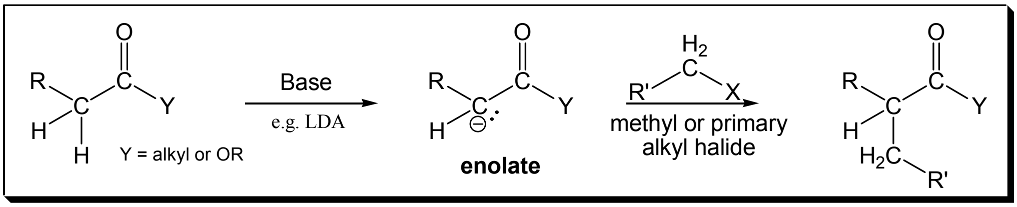
   a. Draw the product that results from the curved arrows shown in Model 2.

   b. Show this same reaction using the other enolate resonance structure (redrawn below).

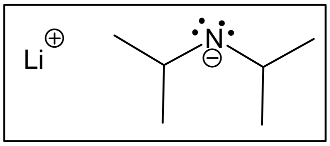


   c. What is the name of this type of mechanism?

Synthetic Transformation 25.1: Base-Promoted α-Alkylation of Carbonyl Compounds



6. Do you expect **LDA** (structure shown at right) to be a strong base, a good nucleophile, or both? Explain your reasoning.



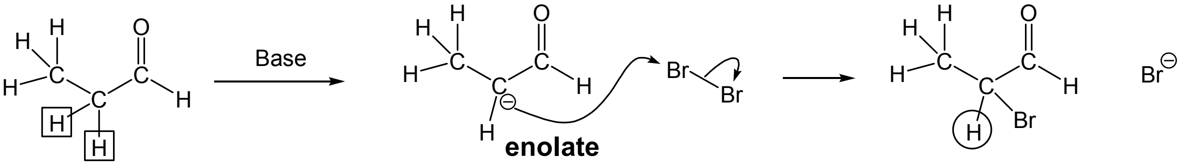
Lithium Di-isopropyl Amide

"LDA"

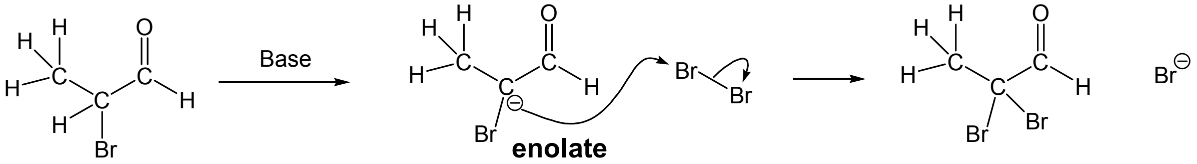
7. (Check your work.) Is your answer above consistent with the fact that LDA is an excellent base for Synthetic Transformation 25.1 because it produces almost exclusively enolate (and does NOT bond to the carbonyl carbon)?

Model 3: Problems with Base-Promoted α-Halogenation

In principle, it should be possible to replace one H_α with a halogen as shown below…



Unfortunately, the product above is more acidic than the starting material so the 2nd H_α is also replaced…



This reaction cannot be controlled and stops only when all alpha hydrogens have been replaced.

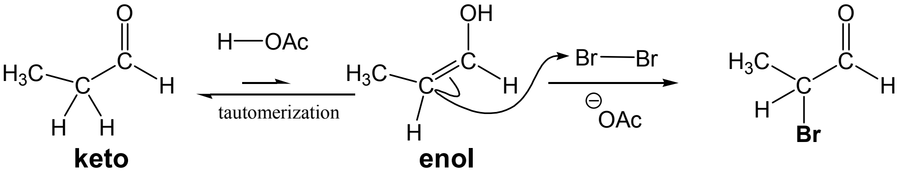
Base-promoted halogenation of methyl ketones leads to an interesting result known as the ***haloform reaction*** *(See Exercises.).*

Critical Thinking Questions

8. Construct an explanation for why the circled H in Model 3 is more acidic than the boxed H's.

Model 4: Acid-Catalyzed α-Halogenation (Enol Nucleophiles)

Mono-α-halogenation can be achieved using acidic (instead of basic) conditions. In acidic conditions the active nucleophile is an enol instead of an enolate.



Critical Thinking Questions

9. Devise a mechanism for the (overall four-step) reaction in Model 4. The active nucleophile in acid (the enol) and one curved arrow (depicting formation of the C—Br bond) are shown for you.

10. In a basic solution of an alcohol, alkoxide (RO^-) can act as a nucleophile, but in an acidic solution of an alcohol RO^- is NOT available; the best nucleophile available for reactions is therefore ROH.

    a. Explain why an alcoxide (RO^-) is NOT found in an acidic solution (*except in trace amounts*).

    b. What is the best nucleophile available for reaction…

        (1) in a **basic** solution of aldehyde?

        (2) in an **acidic** solution of aldehyde? (Check your work: See Models 3 and 4.)

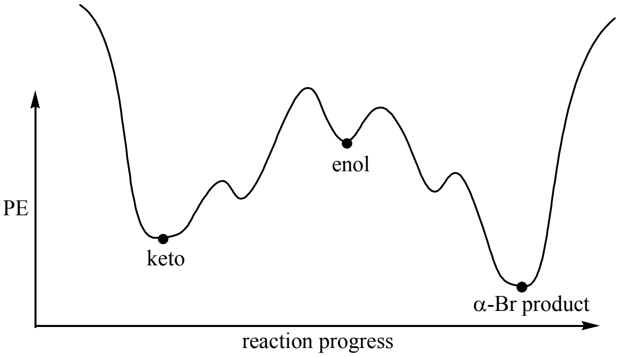
    c. Which is a better nucleophile **RO^-** or **ROH**? (circle one)

    d. Which is a better nucleophile **enolate** or **enol**? (circle one)

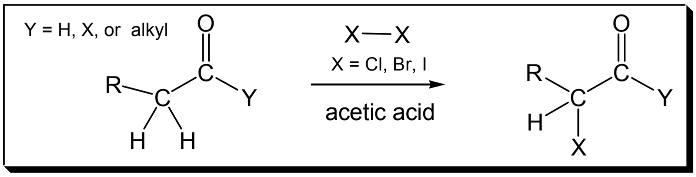
    e. (Check your work.) Is your answer above consistent with the fact that acid-catalyzed α-halogenations are much slower and more controlled than those in basic conditions?

11. Assume 99% of the starting aldehyde in Model 4 is in the keto form. Explain how most of the propanal can be converted to 2-bromopropanal even though, at any given moment, **less than 1% of the propanal in solution is in the enol form.**

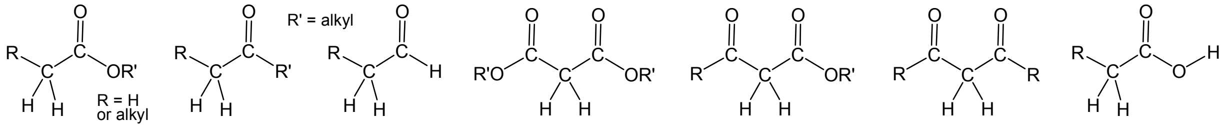
    In other words, what happens once all the propanal that was originally in the enol form has been converted to product?



Synthetic Transformation 25.2: Acid-Catalyzed α-Halogenation of Carbonyl Compounds



Model 5: pK_a Values of Selected Carbonyl Compounds



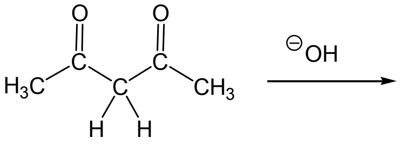
24 19 17 13 11 9 5

Critical Thinking Questions

12. Identify any **beta-keto carbonyl compounds** (β-keto carbonyl compounds) in Model 5. (Recall from Nomenclature Worksheet 4 that a β-keto carbonyl compound has a C=O on the "beta carbon" of a carbonyl functional group.)

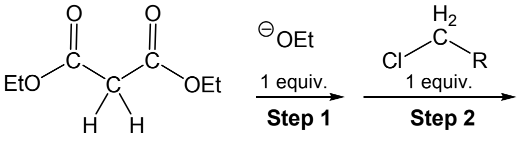
13. Consider the pK_a data in Model 5.
    a. For each compound, circle the H or H's associated with the pK_a value listed below it.
    b. Which is more acidic, **an aldehyde** or **a ketone**? (circle one)
    c. Which is more acidic, **a ketone** or **an ester**? (circle one)

14. Draw the conjugate base of the β-keto ketone below, including all important resonance structures.

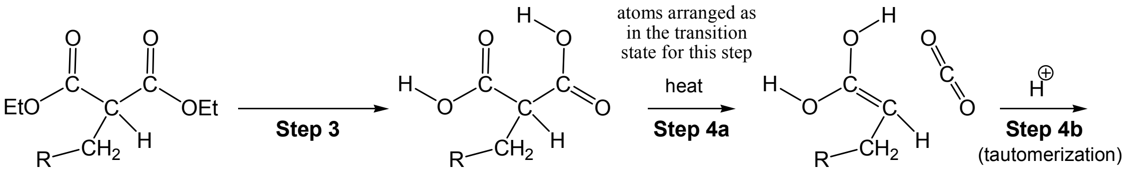


15. Construct an explanation for why the β-keto ketone above (with a pK_a of about 9) is much more acidic than an ordinary ketone (with a pK_a of about 19).

16. Draw the most likely product of the following reaction sequence:

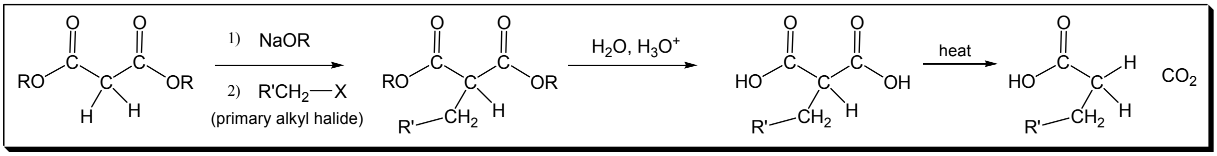


17. The previous question shows the first two steps in a common synthesis of carboxylic acids starting from a β-keto diester (also called a **malonic ester**).



    a. Fill in appropriate reagents over the reaction arrow for Step 3.
    b. Devise a one-step mechanism for Step 4a (called **decarboxylation** = loss of CO_2).
    c. Draw the final carboxylic acid product (the keto tautomer of the enol shown above).

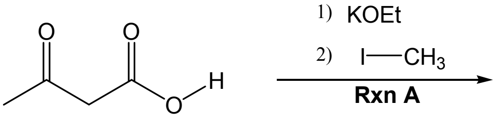
Synthetic Transformation 25.3: Malonic Ester Synthesis of Carboxylic Acids

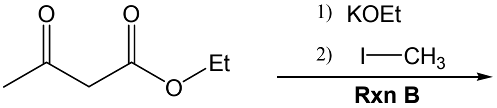


Exercises for Part A

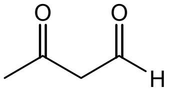
1. Construct an explanation for why it is much easier to remove an H from a carboxylic acid than from an aldehyde.

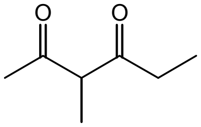
2. Draw the products of Rxn's A and B, below.

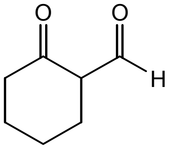


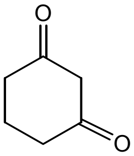


3. Explain why the examples below are called **β-keto** aldehydes or ketones.







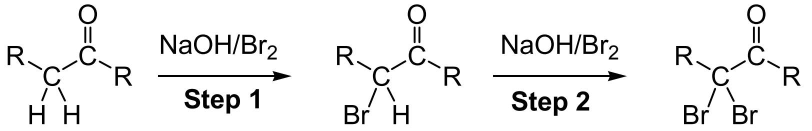


4. The β-keto aldehyde on the far left, above, has three different possible conjugate bases.
   a. Draw all three.
   b. One conjugate base is not resonance-stabilized at all. Which one is this?
   c. Of the two resonance-stabilized conjugate bases, one has a total of two resonance structures, and the other has a total of three. Draw all resonance structures of both.
   d. Draw in the most acidic H (or H's) on each **β-keto** compound in the previous question.

5. Explain why LDA is used in Synthetic Transformation 25.1, but is not needed in Synthetic Transformation 25.3. In other words, explain why a weaker alcoxide base is sufficient to effect the latter transformation.

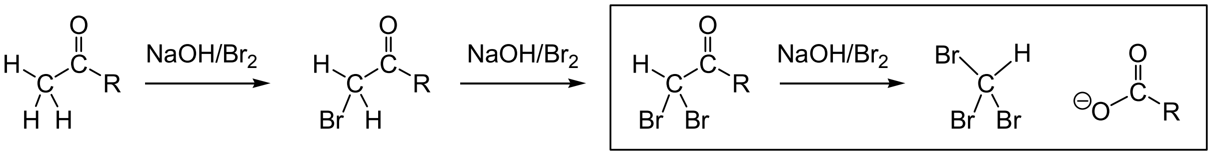
6. Describe how an acid anhydride differs from a β-keto carbonyl compound (such as a malonic ester).

7. Which reaction below is faster, Step 1 or Step 2? Explain your reasoning. (Assume that in each reaction the rate-limiting step is removal of the H by hydroxide.)

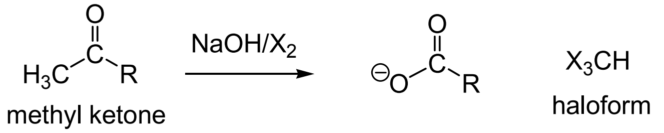


8. Is your answer above consistent with the fact that base-promoted α-halogenations are very difficult to control and usually result in all α-H's being replaced with halogen atoms? Explain.

9. Base-promoted halogenation of a **methyl** ketone (or aldehyde) gives rise to the following (somewhat unexpected) product. Devise a mechanism for the portion of this reaction in the box.



Synthetic Transformation 25.4: Haloform Reaction (and Iodoform Test for Methyl Ketones)



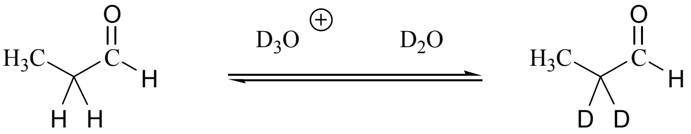
When X = I, the product (I_3CH) is a yellow precipitate. This can be used as an analytical test for the presence of a methyl ketone.

10. Based on the energy diagram in CTQ 11, which is rate-limiting in acid-catalyzed alpha-halogenation, **keto-enol tautomerization** or **halogenation**? (circle one)

11. Assuming your answer above holds true for all acid-catalyzed alpha substitution reactions, which of the following acid-catalyzed reactions (if either) is expected to be faster?
alpha-chlorination or **alpha-bromination** or **neither (rates are the same)** (circle one)

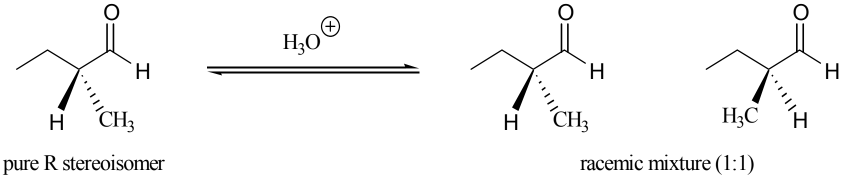
12. Use curved arrows to show the mechanism of an acid-catalyzed tautomerization.

13. Show the mechanism of the following reaction:



14. The reaction in Model 3 is called base-"promoted" halogenation, while the reaction in Model 4 is called acid-"*catalyzed*" halogenation. Explain the use of the different terms in quotes in each case.

15. A solution of pure **R** chiral aldehyde (shown below) was accidentally exposed to a small amount of acid. The next day, the solution was found to contain a racemic mixture (1:1 mix of **R** and **S**). Draw a mechanism to show how conversion of R into S could have occurred.

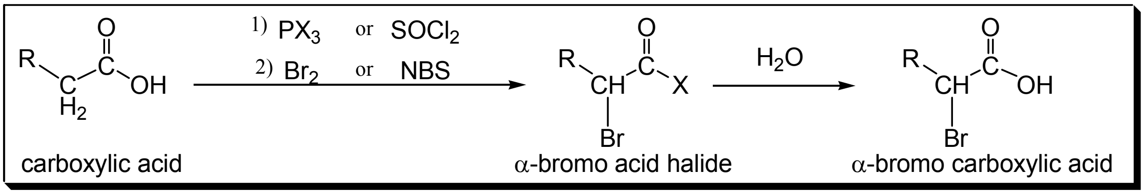


16. Draw the keto form of phenol. Explain why phenol is more stable in its enol form. (Note that phenol is one of the very few aldehydes or ketones for which the enol form is favored.)

17. Both enols and enolates can act as nucleophiles. Which one is a better nucleophile? Under what circumstances does each act as a nucleophile?

18. Acid-catalyzed alpha halogenation does not work for esters, amides, or carboxylic acids, but it does work for acid halides. This fact can be exploited to generate α-brominated carboxylic acid derivatives as shown in Synthetic Transformation 25.5.

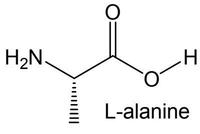
Synthetic Transformation 25.5: α-Bromination of Carboxylic Acids (Hell-Vollhard-Zelinsky)



a. Show the mechanisms of acid-catalyzed bromination of an acid chloride (Assume the reagents are Br_2 and H^+, though the catalyst in the reaction above is a phosphorus species.).

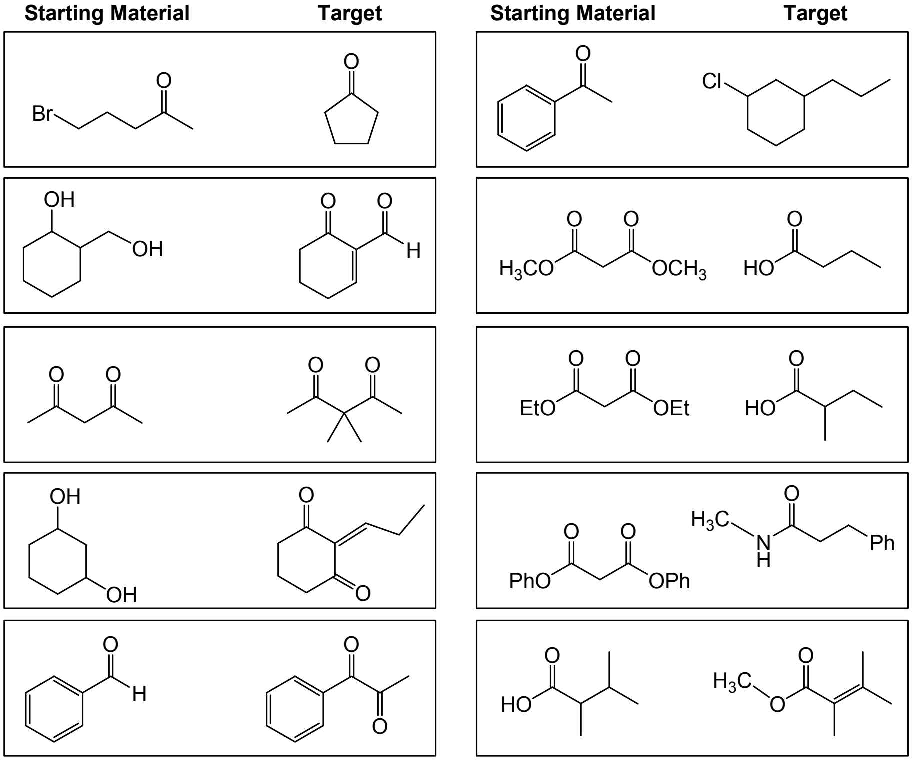
b. What reagents could be used in place of water in the last step of Synthetic Transformation 25.5 to generate a methyl ester? …an *N,N*-dimethyl amide?

19. Alpha-bromination of a carboxylic acid is a critical step in some laboratory syntheses of amino acids. Devise a synthesis of racemic alanine from propionic acid.



20. Explain why the product of the reaction above is racemic alanine, rather than the biologically active S enantiomer, L-alanine.

21. Design a synthesis of each of the following target molecules from the starting material given.



22. Read the assigned pages in your text, and do the assigned problems.

The Big Picture

The two preceding ChemActivities focused on reactions of carbonyl compounds that occur at the carbonyl carbon. This ChemActivity is the first in a series of three that focus on reactions at the alpha carbon. The common theme in all the alpha carbon ChemActivities is that the alpha carbon is nucleophilic, both in basic conditions (via an enolate) and in acidic conditions (via an enol).

The reactions in the current activity are relatively straightforward (and also less important) than those in the upcoming activities. Before moving on, be sure you are quite comfortable with enolate and enol nucleophiles and skilled at keeping track of your carbons in reactions such as the malonic ester syntheses.

Common Points of Confusion

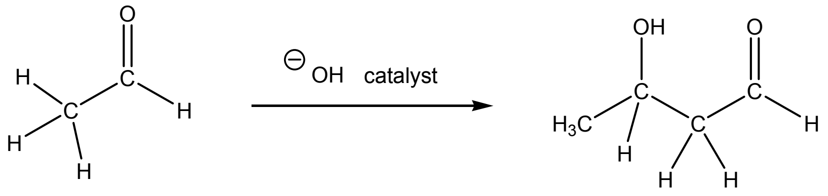
- Many students assume that the H attached to the carbonyl of an aldehyde is most acidic because it seems like the product (with a negative on a carbonyl carbon) must somehow be resonance-stabilized. In fact, only removal of hydrogens **alpha** to a carbonyl give rise to resonance-stabilized conjugate bases of aldehydes or ketones (called enolates).
- A critical skill going forward (even thought it sounds quite *kindergarten*ish) is to count your carbons after each step in a synthesis or mechanism. It is very easy to lose or gain a carbon during the malonic ester syntheses in this ChemActivity and even easier to make such an error in the aldol condensations in the next ChemActivity. **COUNT YOUR CARBONS!**

ChemActivity 26: Aldol and Claisen Reactions

PART A: BASE-CATALYZED ALDOL REACTIONS

(What is the mechanism of a base-catalyzed **aldol reaction**?)

Model 1: Aldol Reaction



acetaldehyde

an example of an "**aldol**"

Critical Thinking Questions

1. Consider the reaction in Model 1.

   a. (E) What two functional groups are found in the product shown in Model 1?

   b. The term aldol is a contraction of “ald” and “ol.” Is this consistent with your answer to the previous question? Explain.

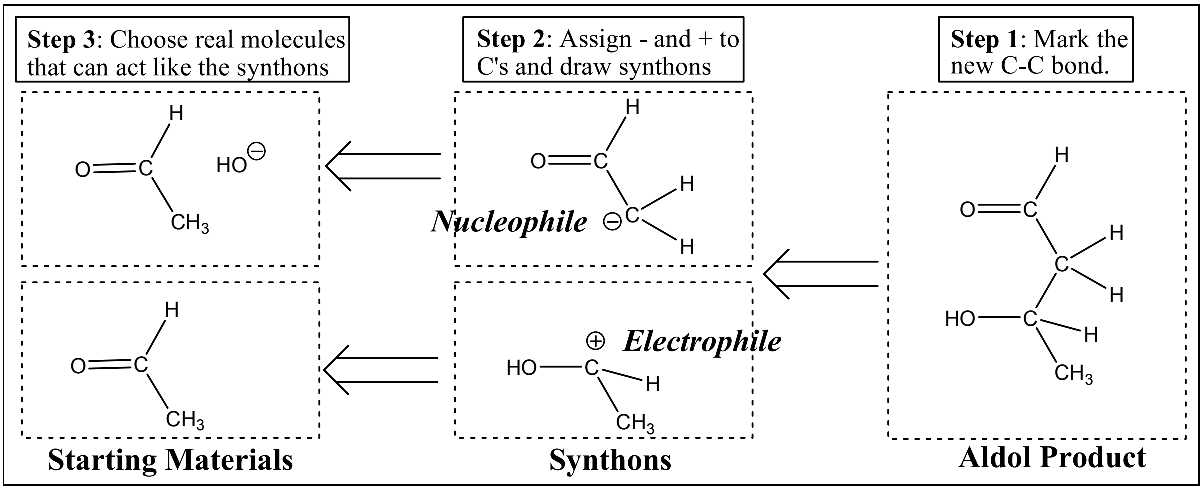
   c. (E) How many carbons are there in the aldol product shown in Model 1?

   d. (E) Assuming all carbons in the product above come from the starting material (acetaldehyde), how many molecules of starting material are required to make one molecule of the product?

   e. Label the **new carbon-carbon bond** in the aldol product, and circle each acetaldehyde **subunit** (= two carbons that were originally an acetaldehyde molecule).

   f. Devise a reasonable mechanism for the reaction in Model 1. *Hint*: In the first step, hydroxide reacts with one molecule of aldehyde to produce a carbon nucleophile as in Mem. Task 25.1.

Model 2: Analysis of an Aldol Product Using Retrosynthesis


Step 3: Choose real molecules that can act like the synthons
Step 2: Assign - and + to C's and draw synthons
Step 1: Mark the new C-C bond.
H
O=C
HO⊖
CH3
Nucleophile
⊖C
H
H
⊕ Electrophile
HO—C
H
CH3
HO—C
Starting Materials
Synthons
Aldol Product

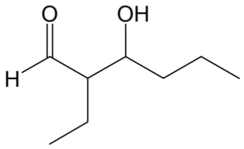
Critical Thinking Questions

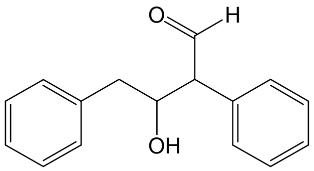
2. On the aldol product above, complete **Step 1** by drawing a line through the new C—C bond.

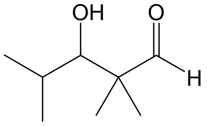
3. Explain how a mixture of acetaldehyde and hydroxide is equivalent to the nucleophilic synthon.

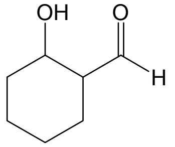
4. In what way is acetaldehyde (by itself) similar to (acts like) the electrophilic synthon shown above?

5. Below each, mark the new carbon-carbon bond, and draw a molecule that could be mixed with NaOH to make the aldol product shown.



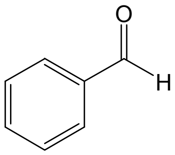


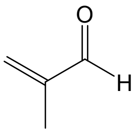


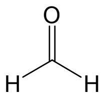


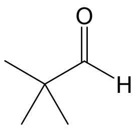
Careful, this one is tricky!

6. Explain why each of the following aldehydes **cannot** participate in an aldol reaction.







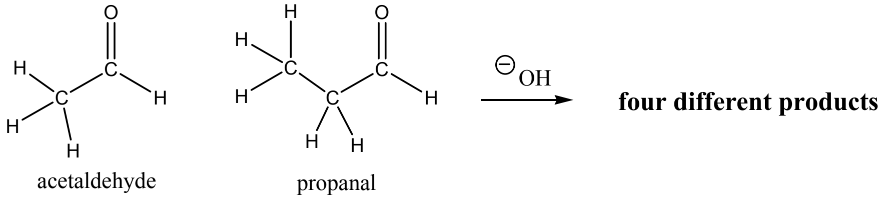


Memorization Task 26.1: An aldehyde must have an H_α to undergo an aldol reaction.

This is because generation of the nucleophile in an aldol reaction involves removal of an H_α.

7. (Check your work.) Is your answer to the previous CTQ consistent with Memorization Task 26.1?

Model 3: Mixed Aldol Reactions

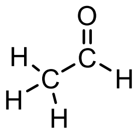
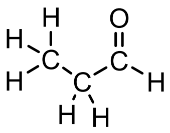
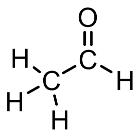
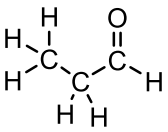


Critical Thinking Questions

8. (E) **T** or **F**: In the presence of hydroxide, either acetaldehyde or propanal can serve as a nucleophile in an aldol reaction.

9. (E) **T** or **F**: Either acetaldehyde or propanal can serve as an electrophile in an aldol reaction.

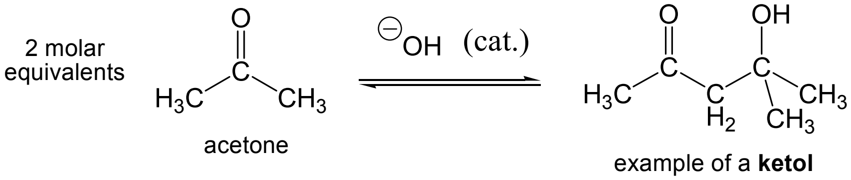
10. Draw the **four products** that result from the mixture in Model 3. *Do not draw the mechanisms.* (The two products marked "**mixed aldol**" result from a combination of two different aldehydes.)

serves as nucleophile ⇨ serves as electrophile ⇩		
	Aldol	Mixed Aldol
	Mixed Aldol	Aldol

11. (Check your work.) Do your group's entries above match the answers of groups sitting near you?

Model 4: “Aldol” Reactions Involving Ketones (“Ketols”?)

Ketones can also participate in aldol-type reactions. The product of such a reaction should technically be called a **ketol** (**ket**one + alcoh**ol**), but such products are usually also called aldol products.



Critical Thinking Questions

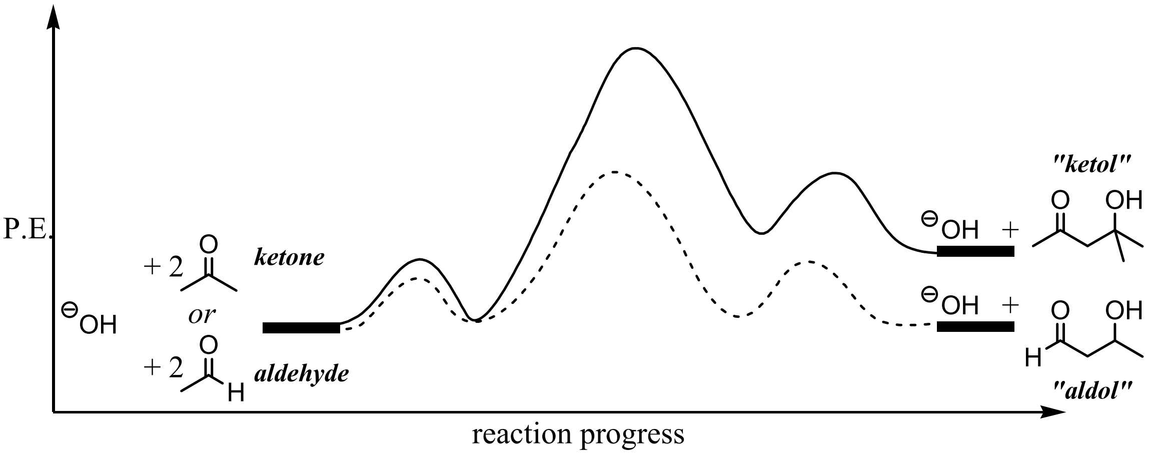
12. Which is a better electrophile, an aldehyde such as acetaldehyde (Model 1) or a ketone such as acetone (Model 4)? Check your work: See Memorization Task 23.1.

13. Is your answer to the previous question consistent with the fact that aldol reactions with aldehydes give much better yields than aldol (ketol) reactions with ketones?

14. Energy diagrams for the reactions in Model 1 (---) and Model 4 (—) are shown below. According to these diagrams…

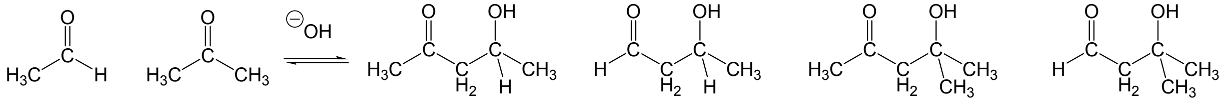
    a. Is the “aldol” reaction in Model 1 **uphill** or **downhill** or **neither** in energy? (circle one)

    b. Is the “ketol” reaction in Model 4 **uphill** or **downhill** or **neither** in energy? (circle one)



15. In a mixed aldol reaction involving acetaldehyde and acetone, only two of the four possible products are observed. Cross out the two products that are unfavorable, and explain your reasoning. (*Hint*: For each product, identify if acetone or acetaldehyde served as the electrophile and nucleophile.)

Two of these four possible products are formed preferentially

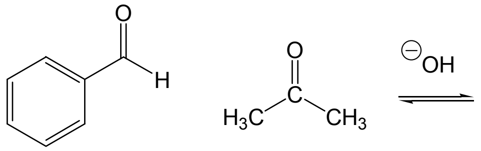


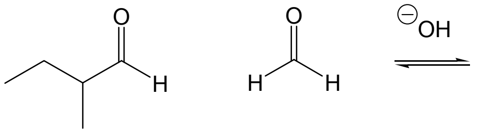
Memorization Task 26.2: In a mixed aldol reaction involving an aldehyde and a ketone…

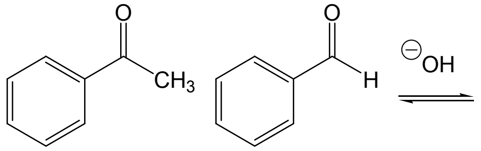
the aldehyde or the ketone can act as the nucleophile (assuming an H_α is available to be removed by the base); however, the aldehyde will out-compete the ketone to serve as the electrophile in the reaction.

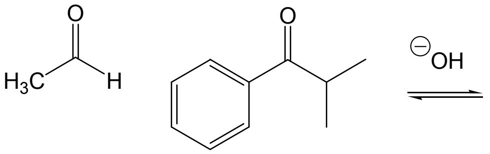
16. (Check your work.) Is your answer to the previous CTQ consistent with Memorization Task 26.2?

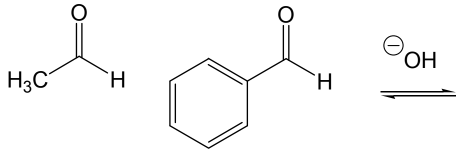
17. For each of the following mixed aldol reaction conditions…
    a. Write "**possible nucleophile**" below each compound that could serve as the nucleophile.
    b. Write "**electrophile**" below the compound that is more likely to serve as the electrophile.
    c. Draw the single most likely aldol product of each reaction.











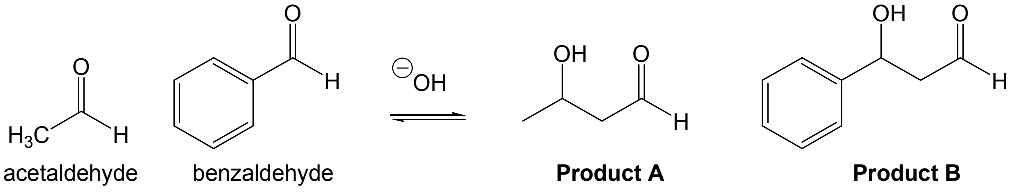
18. (Check your work.) Are your answers above consistent with the fact that the last two reactions give the *same* major product (3-hydroxybutanal) and that, in both these reactions, the aromatic reactant acts as a spectator and is NOT involved in formation of the major product?

PART B: CONTROLLING PRODUCT FORMATION IN ALDOLS

(Why are aldol reactions often called “condensation” reactions?)

Model 5: Controlling Product Formation in a Mixed Aldol

Consider the *last* reaction from the previous page…

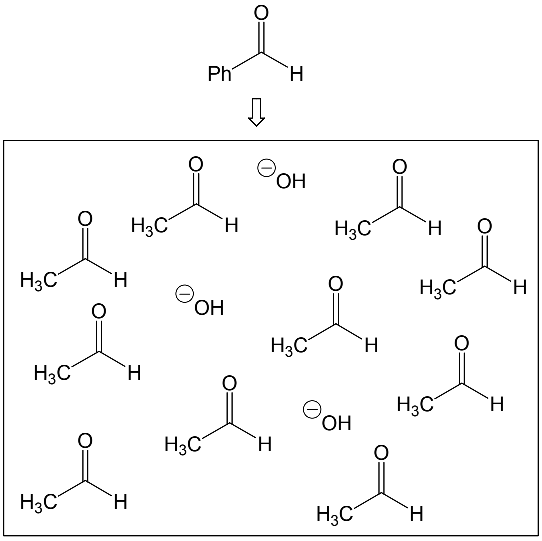


In the mixture above **Product A** is formed preferentially. This is because **acetaldehyde** can serve as both a better nucleophile *and* a better electrophile compared to **benzaldehyde**.

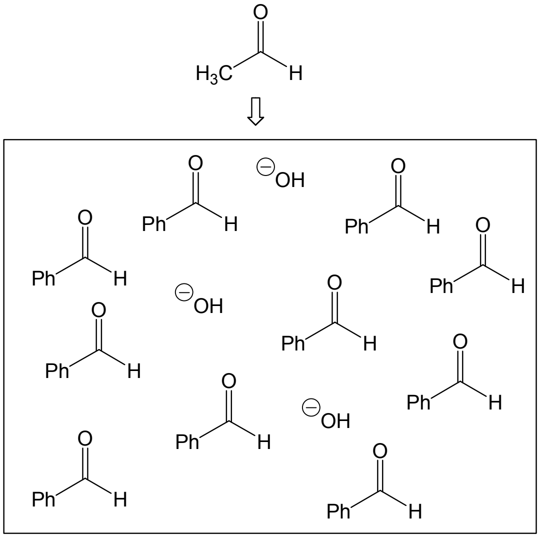
Critical Thinking Questions

19. Using one of the following laboratory procedures you can force benzaldehyde to act as an aldol electrophile and thereby generate **Product B**. Predict which procedure will do this, **(1)** or **(2)**.

(1) A small amount of benzaldehyde is added slowly to a mixture of acetaldehyde & base.



(2) A small amount of acetaldehyde is added slowly to a mixture of benzaldehyde & base.

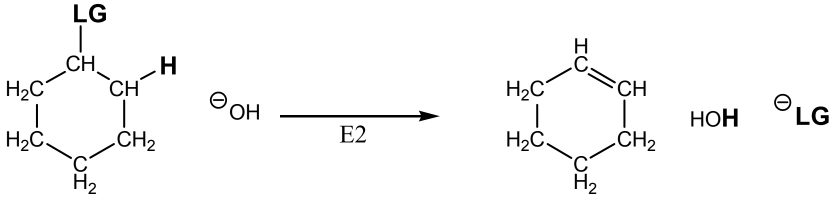


20. (Check your work.) In one of the boxes above, an aldol reaction (leading to **Product A**) will occur even before addition of the second aldehyde. Cross out this box.

21. (Check your work.) In the other box, no aldol reaction can occur *until* a drop of the second aldehyde has been added. Explain.

22. Construct an explanation for why the procedure on the right will selectively produce **Product B**. *Hint*: First explain why Product A is *unlikely* to form in this procedure.

Model 6: (*Review*) Elimination



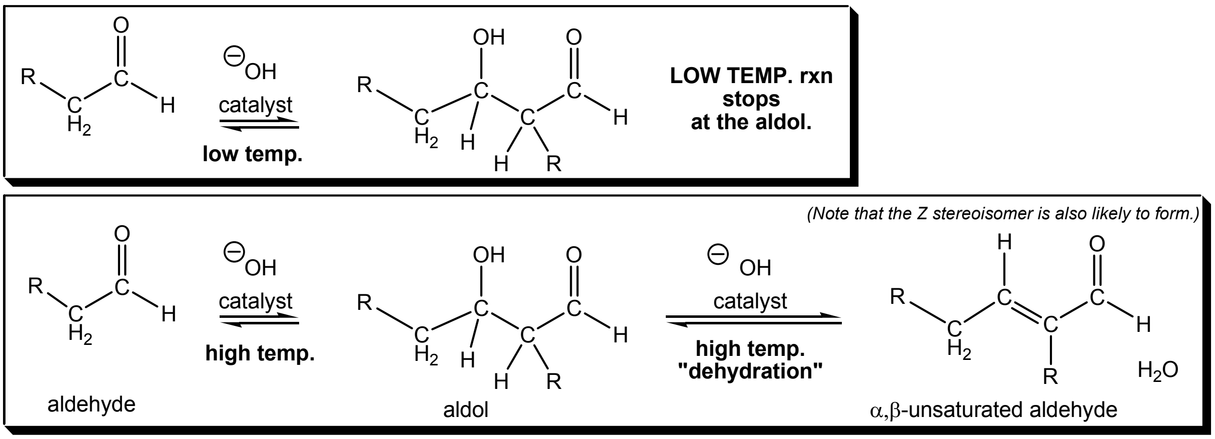
Critical Thinking Questions

23. (*Review*) Use curved arrows to show the mechanism of the reaction in Model 6.
24. (*Review*) What does **LG** stand for, and what is an example of a good LG?
25. (*Review*) Is an E2 reaction **one step** or **two steps** (circle one)?
26. (*Review*) What do the "**E**" and the "**2**" in "**E2**" stand for?

Model 7: Dehydration (loss of H and OH) in an Aldol Reaction

At higher temperatures (above room temperature) an aldol product undergoes an E2 reaction in base.

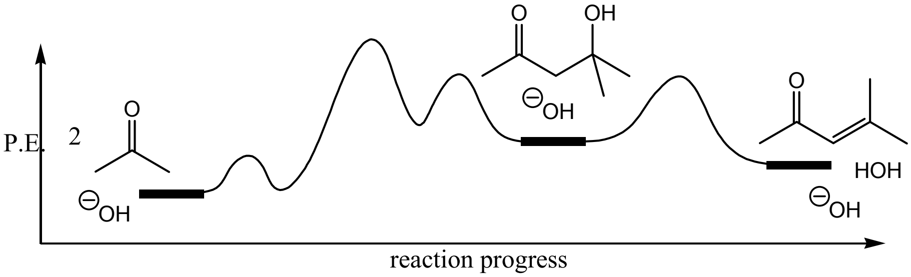
Synthetic Transformations 26.1 and 26.2: Aldol Reaction (Base-Catalyzed)



Critical Thinking Questions

27. (E) Use curved arrows to show the mechanism of the E2 part of the reaction in the box.
    a. (E) What group (that is usually a poor LG) is serving as a leaving group in this E2 reaction?
    b. Construct an explanation for why this step is often called **dehydration** of the aldol.
    c. Researchers first studying aldol reactions noticed that droplets of water ("condensation") sometimes formed on the inside of the flask. Because of this, chemists have come to call aldols, mixed aldols and similar reactions **condensation reactions**. What is the source of these water droplets in an aldol reaction? (*Hint*: They are very common at higher temperatures.)

28. Below is an energy diagram for an aldol (ketol) reaction involving acetone at high temperature.



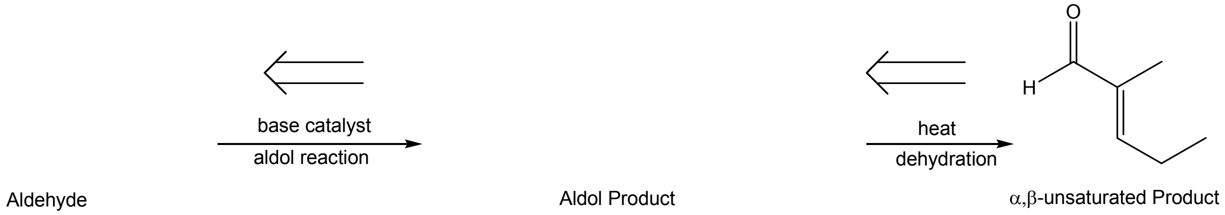
a. (E) Is formation of the α,β-unsaturated product overall, **uphill** or **downhill** in energy?

b. Explain why removing water (boiling it off as steam) will drive this and other condensation reactions to the right to give a very high yield of the α,β-unsaturated product.

Memorization Task 26.3: Dehydration step "drives" a condensation reaction to product

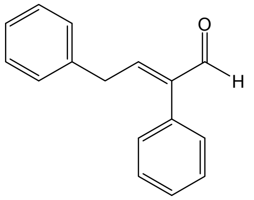
Removal of water as steam shifts the equilibrium of an aldol rxn toward the α,β-unsaturated product.

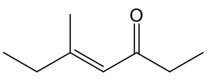
29. For the α,β-unsaturated product below, identify the new carbon-carbon bond that was formed during the aldol reaction (put a line through it), and circle the two aldehyde subunits found in the product.

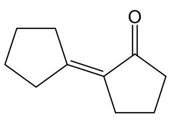


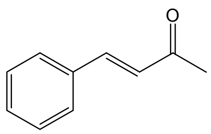
30. Thinking backwards (retrosynthesis), draw the aldol product that precedes the α,β-unsaturated product above right. Then draw the aldehyde starting material for this reaction.

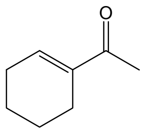
31. Each of the following was made via an aldol reaction. Mark the new carbon-carbon bond, and draw the carbonyl compound (or compounds) that would give each product (upon heating with base).





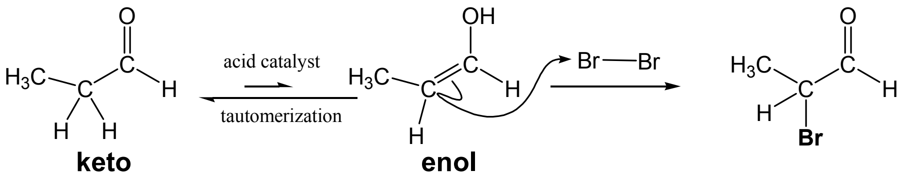




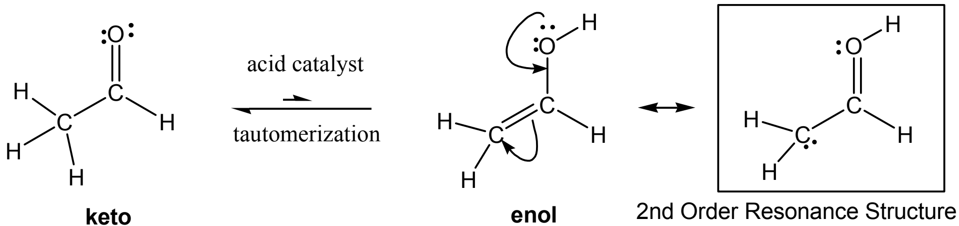


Model 8: (*Review*) Enol as a Nucleophile

Recall that an enol can function as a nucleophile. This occurs in acid, where an enolate cannot form.



The nucleophilicity of the α carbon of an enol can be demonstrated using a 2nd-order resonance structure.



2nd Order Resonance Structure of Enol
(**formal charges missing)**

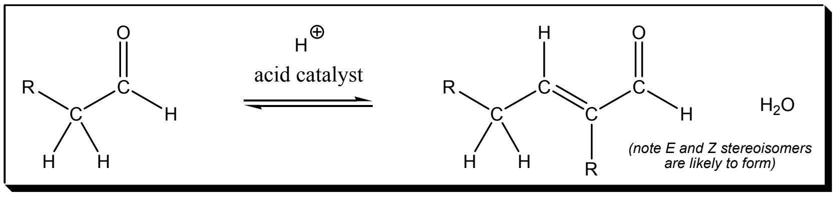
Critical Thinking Questions

32. Add missing formal charges to the 2nd order resonance structure in the box (lone pairs are shown).
33. Explain how this 2nd order resonance structure emphasizes that an enol can act as a nucleophile.

Model 9: Acid-Catalyzed Aldol Condensations

Aldol reactions also work in acidic conditions. However, it is usually **impossible to isolate the aldol product** because, in acid, the reaction tends to go all the way to the α,β-unsaturated carbonyl product.

Synthetic Transformations 26.3: Aldol Reaction (Acid-Catalyzed)



Critical Thinking Questions

34. Use curved arrows to show a mechanism for Synthetic Transformation 26.3. *Hint*: the first step is a tautomerization to generate an enol (it may help to draw a second-order resonance structure of this enol).

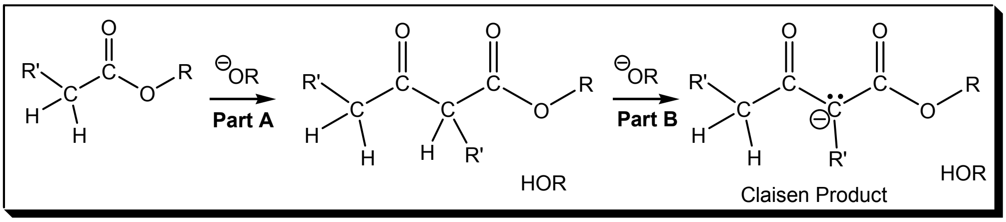
PART C: CLAISEN AND MICHAEL REACTIONS

(What products result when an ester undergoes an aldol-like reaction?)

Model 10: Claisen Reaction

An aldol-like reaction involving an ester is called a Claisen reaction (or a Claisen condensation) named for German chemist Ludwig Claisen, 1851-1930. The final product is a resonance-stabilized anion.

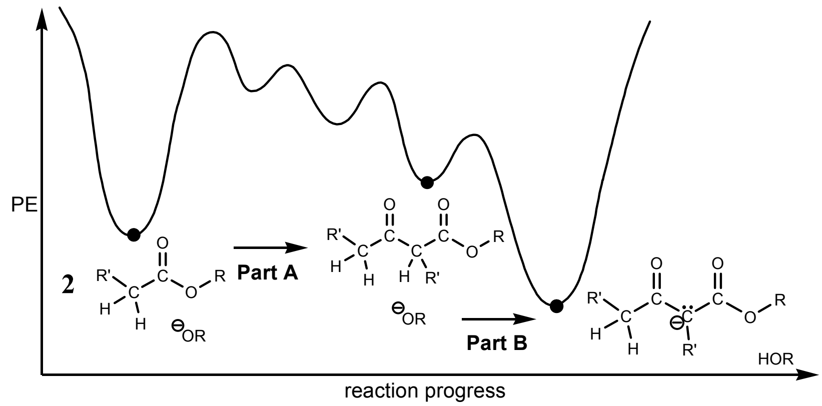
Synthetic Transformation 26.4: Claisen Reaction



Critical Thinking Questions

35. Use curved arrows to show the mechanism of **Part A** of the Claisen reaction in Model 10.

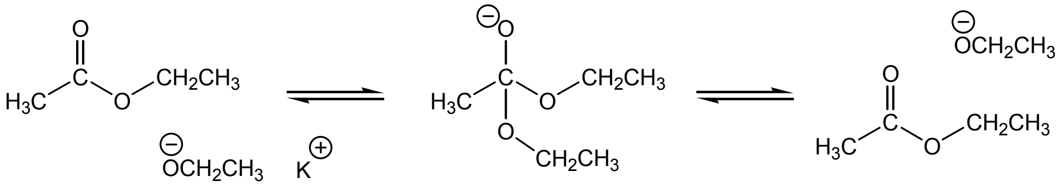
36. (E) Show the mechanism of **Part B** of the Claisen reaction in Model 10.
    a. Draw the other two resonance structures of the Claisen product in Model 10.
    b. Explain why the acid-base reaction in **Part B** is downhill in energy.



Memorization Task 26.4: An ester needs two H_α's for a Claisen to be favorable (downhill).

c. Explain Memorization Task 26.4. (What happens to the 2 H_α's on the nucleophilic ester?)

Model 11: Choosing the Right Base for a Claisen Reaction

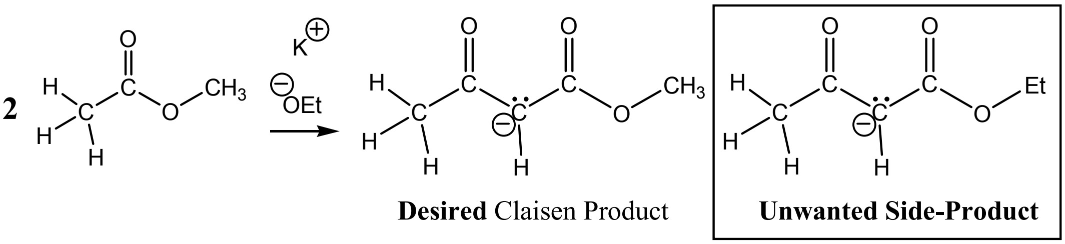


Critical Thinking Questions

37. (*Review*) Add curved arrows to the reaction in Model 11.

38. Is ethoxide ion ($CH_3CH_2O^-$) acting as a **nucleophile** or as a **base** (circle one) in this reaction?

39. A student uses potassium ethoxide in the following Claisen Reaction. The result is the unwanted side product shown in the box.

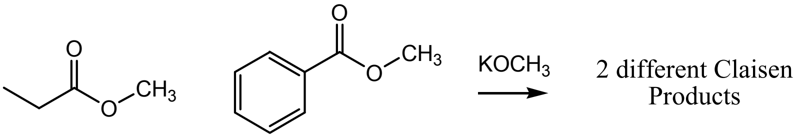


a. Explain how this side product came about.

b. What base should he have used instead of ethoxide ($^-$OEt) to ensure that only the desired Claisen product was produced?

Memorization Task 26.5: R group of the base must match R group of the ester in a Claisen

Model 12: Mixed Claisen Reactions



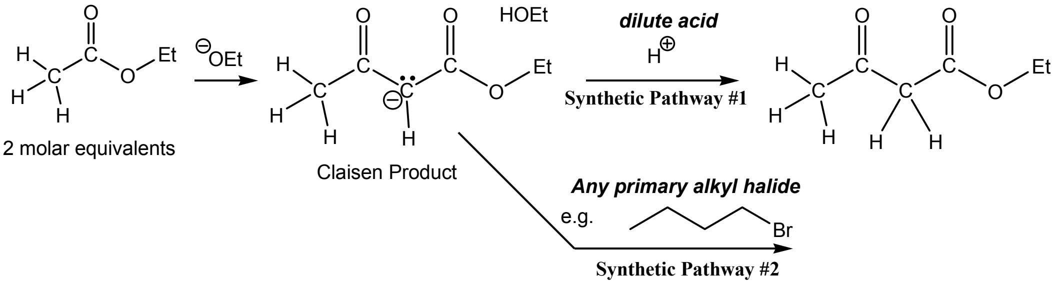
Critical Thinking Questions

40. Place the labels **can be Nuc$^-$** and **can be Elec$^{\delta+}$**, as appropriate, below each ester in Model 12 to show which ester(s) can act as the nucleophile and/or the electrophile in a Claisen reaction.

41. Draw **both** Claisen products that result if the reagents in Model 12 are mixed, and label one of these two products "**mixed Claisen product**" to indicate it was made from two different esters.

42. Suggest a laboratory procedure that gives a high yield of the mixed Claisen product and minimizes the formation of the other Claisen product (the one made from two molecules of methyl propionate).

Model 13: Protonation or α-Alkylation of a Claisen Product



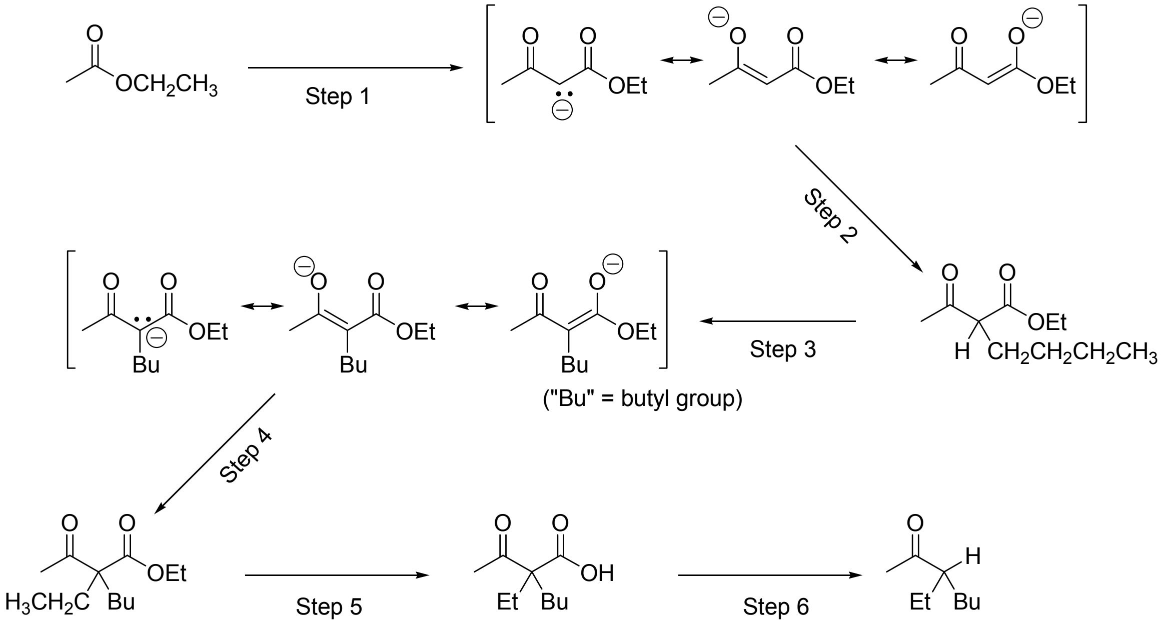
Critical Thinking Questions

43. Add curved arrows to Model 13 to show the mechanism of the reaction in Synthetic Pathway #1.

44. Add curved arrows to show the mechanism of the reaction in Synthetic Pathway #2, and draw the product. (Check your work: This reaction is very similar to Synthetic Transformation 25.1).

45. Explain why the products in Model 13 are called **β-keto** esters.

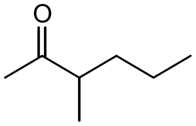
Model 14: Acetoacetic Ester Synthesis of Methyl Ketones



Critical Thinking Questions

46. Above each reaction arrow, write the reagent(s) or conditions necessary for that step in the synthesis. (Note: For some steps, not all products are shown.)

47. This ketone can be made using the strategy in the previous question.

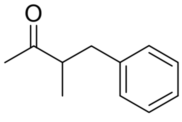


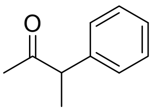
   a. Circle each carbon that that was originally part of the starting ester.

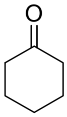
   b. Put a square around each C added during an S_N2 reaction with an alkyl halide (Steps 2 and 4 above), and draw two possible alkyl halides that could have been used to add these carbons.

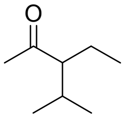
48. Each molecule of the starting ester in Model 14 (ethyl acetate) has four carbons. Since two molecules of ethyl acetate start this synthesis, this means you began with eight carbons. (Check your work in part a of the previous CTQ) The product contains only three of these eight carbons. This means five carbons were lost.
Indicate the steps in Model 14 where each of the missing five carbons was lost.

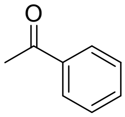
49. Circle the one ketone below that can be made starting from ethyl acetate using the strategy in Model 14, and briefly explain why each of the other ketones cannot be made using this strategy.





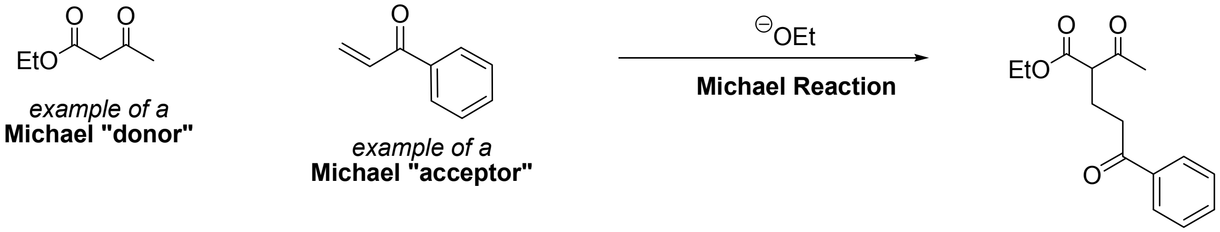






Model 15: Michael Reaction

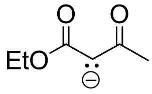
Arthur Michael (1853-1942) developed a reaction in which an extra-stable enolate (of a β-dicarbonyl compound) bonds to the β-position of an α,β-unsaturated carbonyl compound. For example…



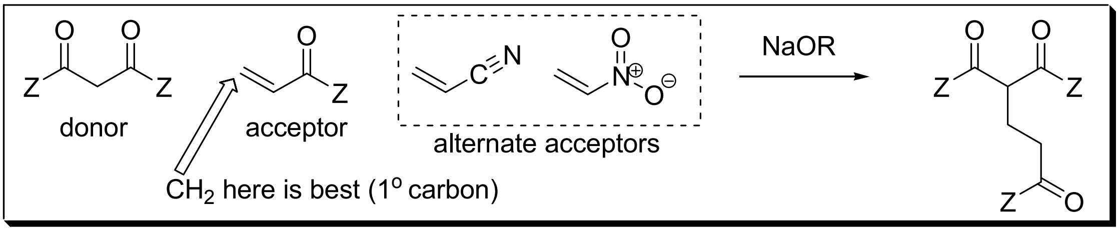
Critical Thinking Questions

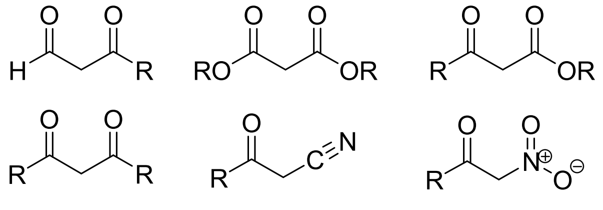
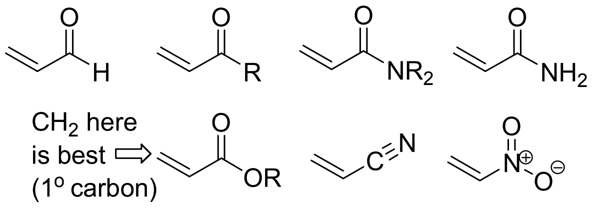
50. Mark the new bond in the Michael product, then devise a mechanism for the reaction in Model 15.

51. Look back at Synthetic Transformation 23.10. Does the enolate nucleophile of a Michael reaction (like the one at right) behave more like a **Grignard reagent** or more like a **lithium dialkyl cuprate reagent** in terms of the regiochemistry of where it bonds to an α,β-unsaturated carbonyl compound? Explain.



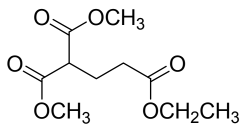
Synthetic Transformation 26.5: Michael Reaction

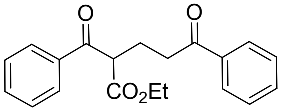


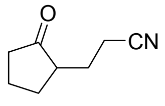
Michael Donors	**Michael Acceptors**
Can be made from almost any β-keto aldehyde, ketone, ester, nitrile or nitro compound, e.g...	*Almost any α,β-unsaturated carbonyl, nitrile or nitro compound (primary carbon is best), e.g...*
	

52. Add the label "**nucleophile"** to one of the boxes above to indicate which type of reactant (donor or acceptor) serves as the nucleophile in a Michael reaction. (Label the other box "**electrophile**.")

53. Mark the new bond in each Michael product, then draw a Michael donor/acceptor pair that could be used to generate that product.

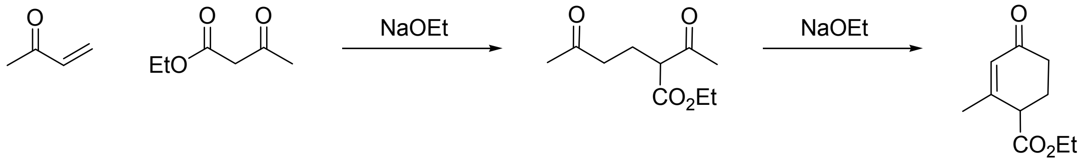






Hint: The initial Michael product was treated with H_3O^+, then decarboxylated to give this product.

54. An **annulation** is a reaction in which a new ring is formed. The **Robinson annulation** is named for English chemist Sir Robert Robinson (1886-1975). It consists of a series of two reactions that use the same catalyst. Under each reaction arrow write the name of a reaction we have studied recently.



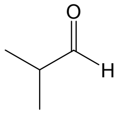
Exercises for Part A

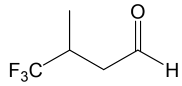
1. Give an example not appearing in this activity of an aldehyde that…

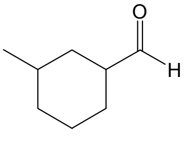
   a. Cannot undergo an aldol reaction.

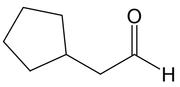
   b. Can undergo an aldol reaction.

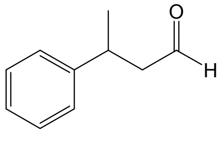
2. For each of the following aldehydes, draw the aldol product that will result when the aldehyde is treated with a catalytic amount of base (e.g., KOH).

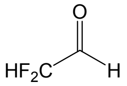




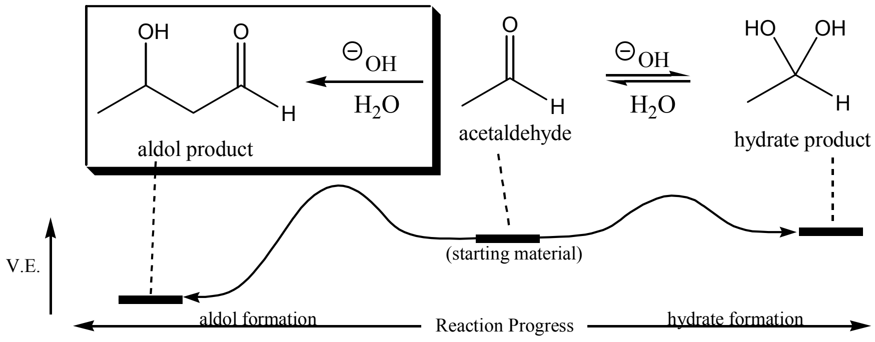








3. The reactants from Model 1 are drawn below. Hydroxide is both a strong base and an excellent nucleophile. As a result, hydrate formation is in competition with aldol formation.

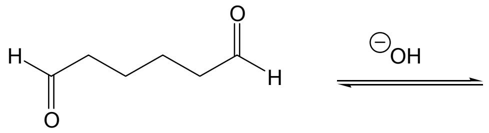


   a. Use curved arrows to show the mechanism of **hydrate** formation.

   b. According to the energy diagram, which is faster, aldol formation or hydrate formation?

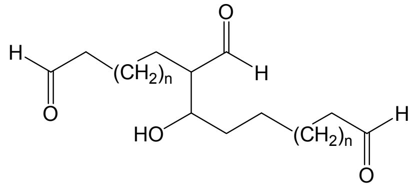
   c. Despite the fact that hydrate formation is faster than aldol formation, at equilibrium there is more aldol than hydrate. Explain.

4. Draw the aldol product that results from an intramolecular aldol reaction involving a base catalyst and this dialdehyde.



   a. Explain why, *a dilute solution of a dialdehyde,* favors formation of a cyclic product over a product like the one shown below, right.

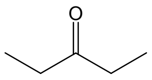
   b. If n >3, a *concentrated* solution of a dialdehyde can give the product shown at right, or even longer chains (polymers). Explain this finding.

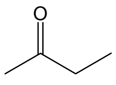


5. Draw the two different aldol products that result from intramolecular aldol reactions involving the di-aldehyde 3-methylhexanedial and base. For each product indicate which aldehyde of the dialdehyde acted as a nucleophile and which acted as an electrophile. Call the ends the **1-aldehyde** and the **6-aldehyde**.

6. Draw the mechanism of the reaction in Model 4.

7. Forming an aldol from a ketone (also called a ketol) is generally unfavorable. However, in Part B we will learn a means of pushing such reactions (though we will not isolate the ketol itself). Draw an aldol/ketol for each ketone. For ketones marked with a "**2**" draw two different products that are constitutional isomers (ignore stereoisomerism).





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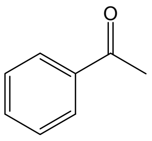

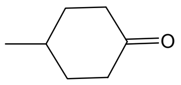

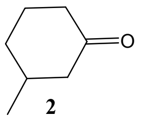

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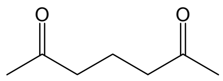
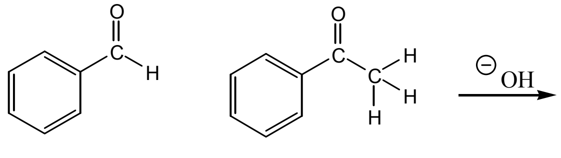


assume formation of a fou-member ring is unfavorable

8. Draw a ketone not appearing above that could give rise to two different aldol/ketol products, and explain your reasoning.

9. Explain why benzaldehyde cannot act as a nucleophile in an aldol reaction.

   a. Which will better serve as an **electrophile** in an aldol reaction: **benzaldehyde** or **acetophenone**?



benzaldehyde acetophenone

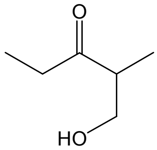
   b. Complete the reaction above by drawing the mechanism leading to the **single** most likely aldol or mixed aldol product.

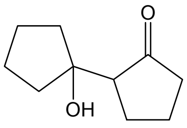
10. Draw a pair of aldehydes and/or ketones (not appearing elsewhere) that would give…

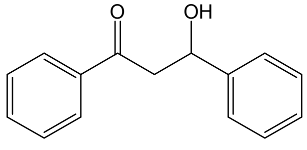
    a. a mixture of four different aldol products and draw each product.

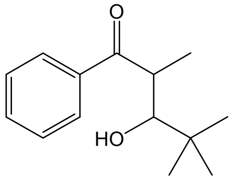
    b. a high yield of a single aldol product and draw the product.

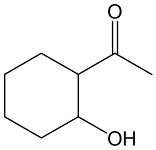
11. **Use retrosynthesis** to draw aldehyde(s) or ketone(s) that could be used to make each aldol product.



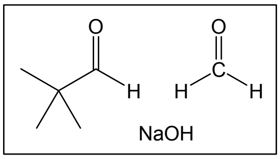


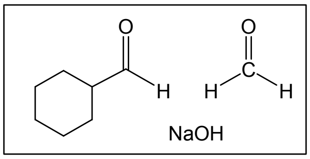


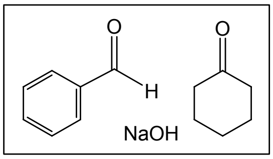


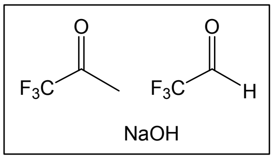


12. Draw the most likely product for each set of reactants or write NO REACTION.

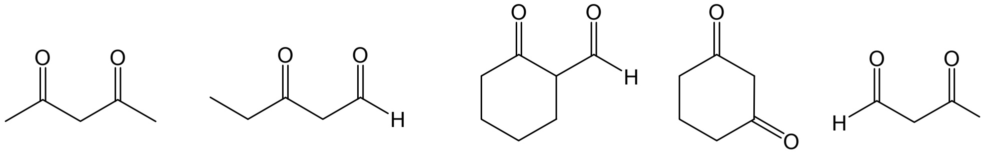








13. The following are called β-keto carbonyl compounds. Construct an explanation for this name.



a. Draw in the most acidic H or H’s (if there is a tie) on each β-keto carbonyl compound.

b. Draw the conjugate base of each molecule above, including all important resonance structures.

c. Which is more acidic, the compounds above or an ordinary aldehyde/ketone such as propanal?

d. Is your answer above consistent with the pK_a data on the table at the end of this book?

e. In a solution of pentane-2,4-dione, propanal, and base, the mixed aldol product is favored because propanal is a better electrophile, and pentan-2,4-dione is more likely to form a nucleophilic enolate. Draw this product, and show the mechanism of formation.

14. Read the assigned pages in your text, and do the assigned problems.

Exercises for Part B

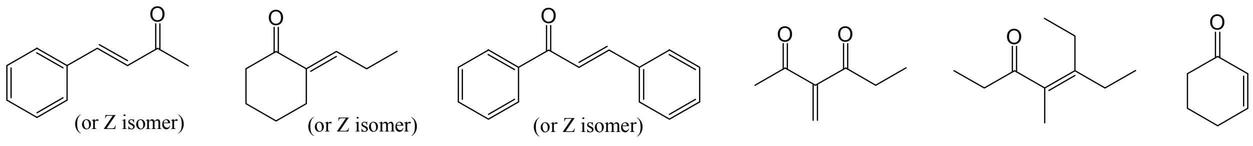
15. Draw an example not appearing in this activity of two different aldehydes or ketones that would give a high yield of a single mixed aldol product only when one is slowly added to the other plus base. Specify which carbonyl compound should be added slowly to the other, and draw the product.

16. Construct an explanation for the name "α,β-unsaturated aldehyde" in Model 7. *Hint*: Which C’s will add an H if you treat it with H_2/Pt so as to “saturate” it with the maximum number of H’s?

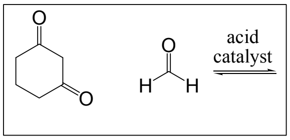
a. What atoms are lost from an aldol in going to the α,β-unsaturated aldehyde?

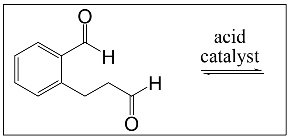
b. Draw the Z stereoisomer that is also formed in the aldol reaction in Model 7.

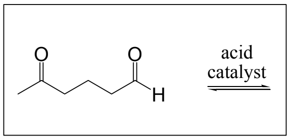
17. Use retrosynthesis to determine starting materials that will give rise to each product.

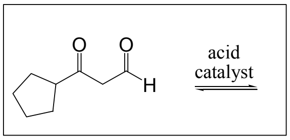


18. Draw the product(s) of each of the following acid-catalyzed aldol reactions.









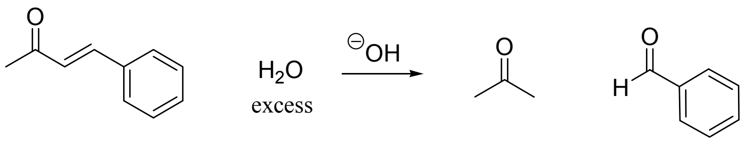
19. Draw all four products that can result when 2-butanone is heated in base at 50°C (RT = 25°C).

20. Explain the following results. When cyclohexanone is treated with base at room temperature a product with molecular formula $C_{12}H_{20}O_2$ is recovered in 22% yield. However, when cyclohexanone is treated with acid at room temperature a product with molecular formula $C_{12}H_{18}O$ is recovered in 92% yield.

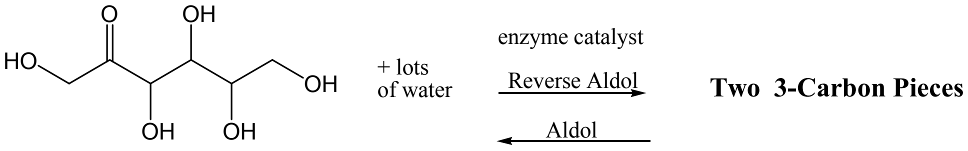
21. In some cases the dehydration step of an aldol reaction is very downhill so it is nearly impossible to isolate the aldol product. The reaction between benzaldehyde and acetone is such an example:
    a. Draw the aldol product and the α,β-unsaturated carbonyl product (both E and Z will form).
    b. Construct an explanation for why the α,β-unsaturated carbonyl products are much more stable than the aldol product. (The aldol product cannot be isolated in this case, even if the reaction is run at very low temperature.)

22. Even in acid or hot basic conditions a mixture of benzaldehyde and 2,4-dimethylpentan-3-one gives a very low yield of a single aldol product instead of an α,β-unsaturated carbonyl product.
    a. Draw the most likely aldol product that results from this mixed aldol reaction.
    b. Construct an explanation for why, in this case, the α,β-unsaturated carbonyl compound cannot form under any conditions, and even attempting to drive the reaction to the right by boiling off water does not work.

23. One very important thing to remember about the aldol reaction is that it can be **undone**. (It is a reversible reaction.) Draw the mechanism of the reaction below (a reverse aldol).



24. Biological systems use aldol-type condensation reactions to make and break carbon-carbon bonds. For example, plants build fructose (and other six-carbon sugars) from smaller pieces using aldols. Animals (such as ourselves) eat the plants and begin the digestion of fructose by doing a **reverse aldol reaction**, breaking it back into three-carbon pieces.



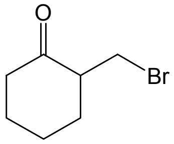
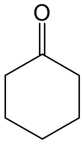
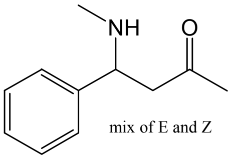
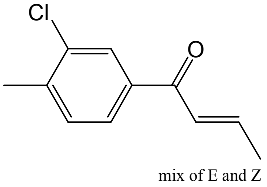
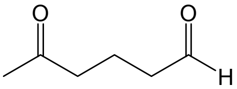
Fructose

    a. Fructose is a complicated-looking molecule, but really **it is an aldol in disguise**. Circle the carbonyl and the one OH group on fructose that are positioned like the C=O and OH of an aldol product.
    b. **DIGEST fructose into two pieces!** That is, draw the structures of the two three-carbon pieces into which we break down fructose (and from which plants can make fructose).

25. The preparation of α,β-unsaturated carbonyl compounds is a subject of great interest among synthetic organic chemists. The aldol method is perhaps the most elegant way to generate such molecules, but there are other ways. Design a synthesis of but-2-enal from butanal.

26. Certain compounds rearrange in acidic or basic solution to form α,β-unsaturated carbonyl compounds. Use curved arrows to construct a mechanism for the rearrangement in base (HO^-), then in acid (H_3O^+) of pent-4-en-2-one into pent-3-en-2-one. (What is the driving force for this?)

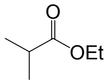
27. Design an efficient synthesis of each of the following target molecules. All carbon atoms must come from the starting material(s) given. Be sure to specify the conditions of any aldol reactions.

Target				
Starting material	cyclohexanone formaldehyde		acetone benzaldehyde methyl amine	toluene acetaldehyde

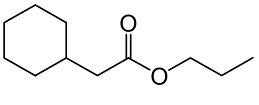
28. Read the assigned pages in your text, and do the assigned problems.

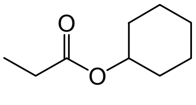
Exercises for Part C

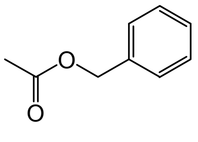
29. Explain why the ester at right does not undergo a favorable (overall downhill) Claisen Reaction. (*Hint*: See Memorization Task 26.4.)



30. What base would you add to each of the following esters to cause a Claisen Reaction?



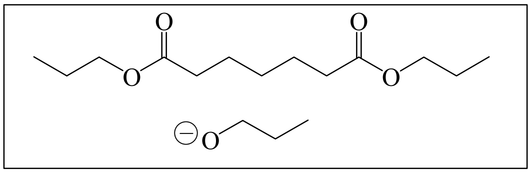


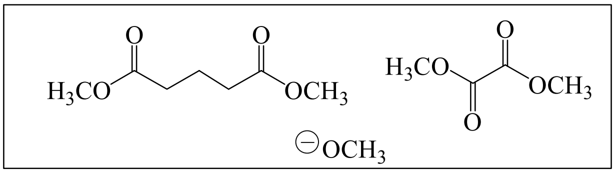


a. Show the mechanism of the Claisen Reaction involving the ester on the far right above.

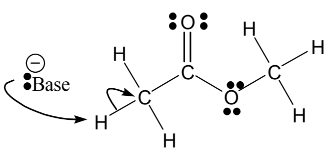
b. Draw the Claisen product that would result with each ester in the previous question

31. Each set of boxed reactants yields a major product that includes a five- or six-member ring. For each box, draw the best mechanism leading to ring formation.

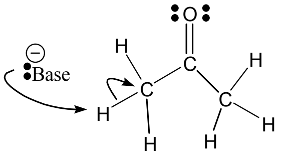




32. Based on what you learned about EAS-directing effects, which is a stronger **electron-donating group**, an OR group or an R group? (Where R is an alkyl group such as methyl, ethyl, etc.)



Ester (methyl acetate)



Ketone (acetone)

a. Which reaction above is more favorable? Explain your reasoning.

b. Which is more acidic: an ester or a ketone?

c. Is your answer consistent with data on the pK_a table at the end of this book?

Memorization Task 26.6: Aldehydes and ketones are more acidic than esters

Because of this fact, in a mixture containing an aldehyde/ketone and an ester, the aldehyde/ketone is more likely to serve as the nucleophile in a **Claisen-type reaction**.

Note that even though aldehydes and ketones are better electrophiles than esters, the dominant product in such a mixture will usually form via the ester acting as an electrophile. This is because, when an ester acts as an electrophile, a β-dicarbonyl product can form, resulting in the downhill and exothermic loss of the acidic hydrogen alpha to BOTH carbonyl groups. This drives the reaction toward the Claisen product.

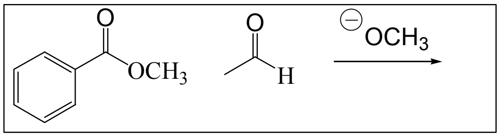
33. Because aldehydes and ketones are more acidic than esters, in a mixture containing an aldehyde or ketone and an ester, the aldehyde/ketone will act as the nucleophile in a Claisen-type reaction.

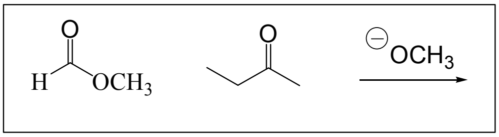
a. Draw the mechanism of a Claisen-type reaction between acetaldehyde and ethyl formate.

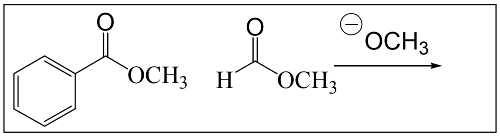
b. Draw the aldol product that will also form from this reaction mixture.

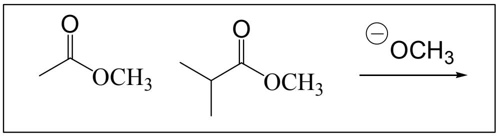
c. Acetaldehyde is such a good electrophile that it may generate significant amounts of the aldol product. Suggest a laboratory procedure that will nearly eliminate formation of the aldol product from the reaction mixture and maximize the yield of the Claisen product.

34. For each of the following reaction mixtures, list the number of different products that could occur via carbon-carbon bond formation (aldol, Claisen or some mixture).



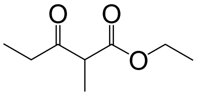


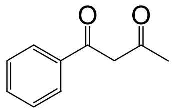


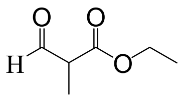


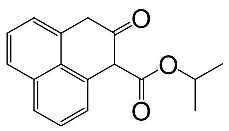
35. Draw the products in the previous question in which an ester acts as the electrophile.

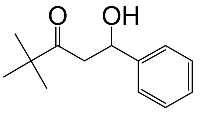
36. Each of the following is the product of an aldol or Claisen-type reaction that has been neutralized with dilute acid. Use retrosynthesis to determine which combination of starting aldehydes, ketones, or esters gave rise to each product, and indicate a suitable base for each reaction.

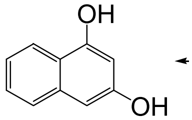






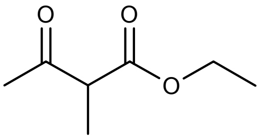


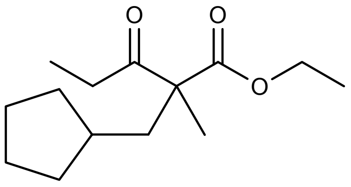


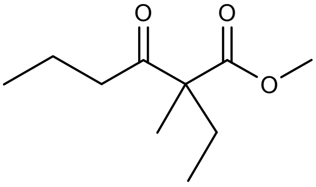


(Hint: This molecule adopts a "double enol" form so as to be aromatic.
Draw the "double keto" form and consider how this could have been made.)

37. Each target is the product of a Claisen Reaction between two identical esters followed by addition of an alkyl halide. Determine the starting ester and alkyl halide.



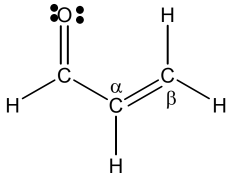




38. Design a synthesis of 3-ethylpentan-2-one using any alkyl halide (with no other functional groups) and any ester (with no other functional groups).

39. Describe key ways in which a Michael addition is like an aldol reaction and key ways in which it is different from an aldol reaction.

40. Draw all reasonable second-order resonance structures for the following α,β-unsaturated carbonyl compound. ***Note: Oxygen must always have an octet, even in a second-order resonance structure!***

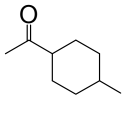


   a. Use these to predict whether the β carbon will be **nucleophilic** or **electrophilic**.

   b. Is your prediction consistent with how such a compound behaves in a Michael reaction?

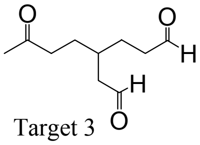
41. Draw the mechanism of the **Robinson annulation** shown in the last CTQ of Part C.

42. Use retrosynthesis to design a way of making each of the following target molecules. The starting materials must include an acetic ester such as ethyl acetate.



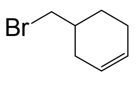
Hint: Use 3-methyl-1,5-dibromopentane in your synthesis.

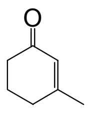
Target 2



Target 3

Hint: Use

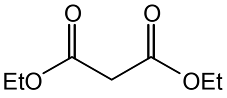




Hint: The last step is an intramolecular aldol (in acid).

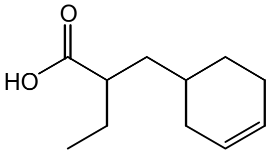
Target 4

43. Use retrosynthesis to design a way of making each of the following target molecules. The starting materials must include ethyl malonate (shown below).

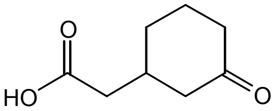


Ethyl Malonate

OEt = OCH_2CH_3



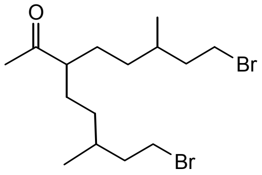
Target 5



Target 6

Hint: involves a Michael Add'n

44. If you use very high concentrations of 3-methyl-1,5-dibromopentane in the synthesis of Target No. 2, the following side product will also occur. Explain why Target No. 2 is favored over this side product at normal or low concentrations.



45. Read the assigned pages in your text, and do the assigned problems.

The Big Picture

Aldol and Claisen reactions will test your ability to keep bonds and atoms straight. All the chemistry found in this chapter has been introduced elsewhere (e.g., enol and enolate nucleophiles, addition-elimination, E2 reactions). The challenge is to apply these to this more complicated environment. One key, as indicated below, is to count your carbons at each step in a synthesis or mechanism.

Aldols, Claisens and related reactions are significant because (unlike reactions involving Grignards, cyanide or other toxic reagents) they provide a way to make and break carbon-carbon bonds in mild conditions. In fact, biological systems use enzyme-catalyzed versions of these reactions for assembling (and disassembling) the carbon backbones of biomolecules. Look for these reactions in any metabolic pathway where the number of carbons changes.

Common Points of Confusion

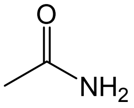
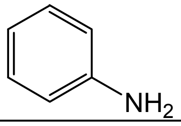
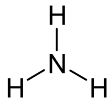
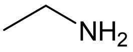
- Count your carbons!! Get in the habit of counting the number of carbons in the starting material and making sure that all carbons are accounted for in the products. Accidentally losing or gaining a carbon is very easy to do in an aldol or Claisen reaction, and especially in a Michael reaction.
- The reactions in this chapter involve combining multi-atom molecules. A good strategy is to draw the product as a simple combination of the reactants, even if this means distorting bond lengths and angles. After you have done this you can "clean up" your drawing by redrawing the product with more accurate angles and lengths.
- Retrosynthetic analysis of an aldol or Claisen product is easier if you first identify the new carbon-carbon bond. For dehydrated aldol (condensation) products this is the C=C double bond.
- Some students confuse **retrosynthesis** with a reverse reaction, especially in the case of aldol reactions, because aldol reaction are **reversible**. Retrosynthetic analysis of an aldol product is a thought exercise used to figure out which aldehydes or ketones must be combined to make the target. A reverse aldol reaction is an actual reaction in which the product is hydrolyzed, using water and a catalyst, back into the aldehydes or ketones that were used to make it.

ChemActivity 27: Amines

(How can you make a primary **amine** from ammonia?)

Model 1: pK_a Values for Various Nitrogen Compounds

It is useful to think of base strength as a measure of the likelihood of a lone pair to make a bond to H^+.

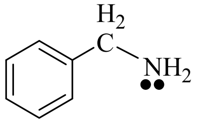
	acetamide (an amide)	aniline (an aromatic amine)	ammonia (simplest amine)	ethyl amine (a 1° amine)
				
pK_a of conjugate acid	0	4.6	9.3	10.8

Critical Thinking Questions

1. (E) Draw in any lone pairs on the structures in Model 1.
2. (E) According to the pK_a data in Model 1, which nitrogen compound is most basic? …least basic?
3. In general, alkyl groups (such as the Et group on ethyl amine) are electron-donating.
   a. Given this, construct an explanation for why the lone pair on ethyl amine is more likely to make a bond to H^+ than the lone pair on ammonia.
   b. Draw **di**ethyl amine, a secondary (2°) amine, predict whether diethyl amine is a **stronger base** or **weaker base** (circle one) than ethyl amine.
   c. (Check your work.) Is your answer above consistent with the fact that the conjugate acid of diethyl amine has a pK_a of 11.0? Explain.
4. Draw one or more second-order resonance structures that help explain why the lone pair on an aromatic amine (such as aniline) is unlikely to form a bond to H^+ compared to ordinary amines such as ammonia, in which the lone pair is **localized** on the nitrogen.

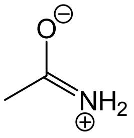
a. Predict if the pK_a of the conjugate acid of the aromatic compound at right is **closer to 10** or **closer to 5**. (Circle one and explain your reasoning.)

"benzyl amine"

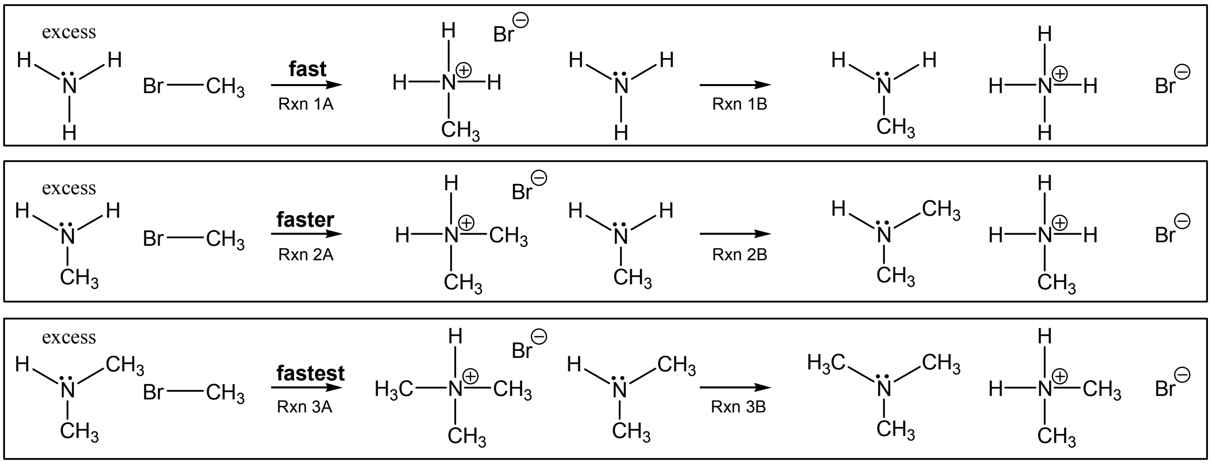


b. (Check your work.) Is your answer above consistent with the fact that benzyl amine is NOT considered an "**aromatic amine**." Explain.

5. Second-order resonance structures are *usually* not as important as ordinary (first-order) resonance structures. In the case of amides, however, there is a second-order resonance structure—shown at right—that is of equal importance to the first-order resonance structure (shown in Model 1). Use this second-order resonance structure to explain why amides are very weak bases.



Model 2: Amine Alkylation



Critical Thinking Questions

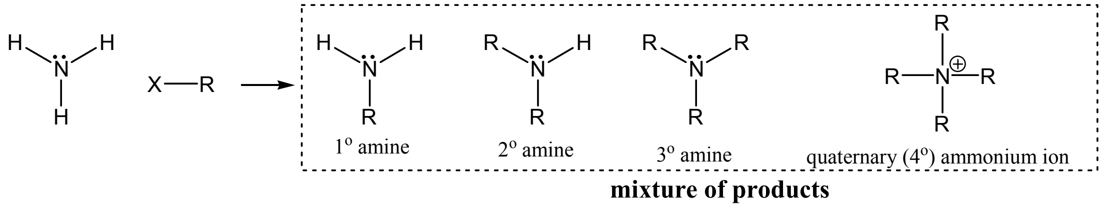
6. (Review) Use curved arrows to show the mechanism of Rxn 1A and Rxn 1B in Model 2.

7. (E) Label each of the starting amines in Model 2 as 3° (tertiary), 2° (secondary), 1° (primary), or 0° (ammonia).

8. Construct an explanation for why the rate of Rxn 3A > rate of Rxn 2A > rate of Rxn 1A. (*Hint*: See pK_a data in Model 1.)

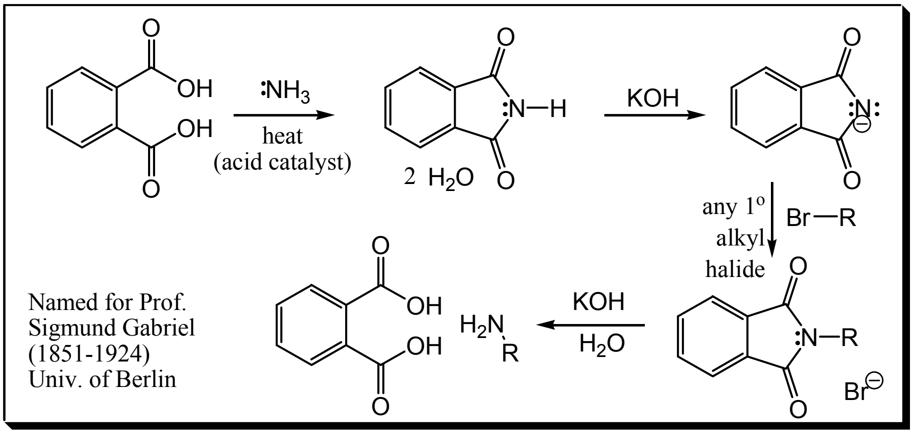
Memorization Task 27.1: Direct alkylation of an amine is not synthetically useful.

Because a 2° amine is a better nucleophile than a 1° amine, and a 1° amine is a better nucleophile than ammonia, the products of Rxns 1A, 1B and 1C on the previous page will compete with the starting material for reaction with alkyl halide (e.g., methyl bromide). The result is a mixture of all possible products, including the quaternary (4°) ammonium salt shown below. For this reason direct alkylation of an amine is not a synthetically useful option for making primary, secondary or tertiary amines.



Model 3: Selective Synthesis of 1°, 2°, and 3° Amines

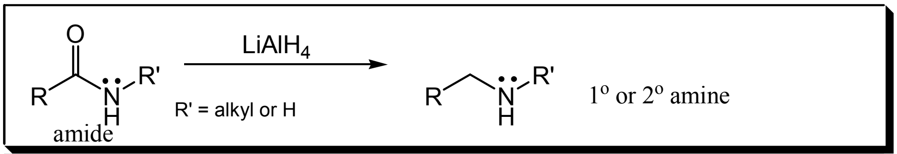
Synthetic Transformation 27.1: Gabriel Synthesis of Primary (1°) Amines



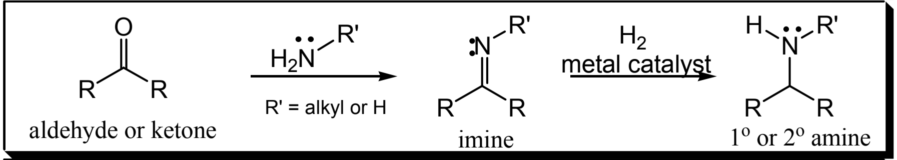
Named for Prof.
Sigmund Gabriel
(1851-1924)
Univ. of Berlin

Synthetic Transformations 27.2-4: Reduction of Amides, Aldehydes, Ketones or Nitriles

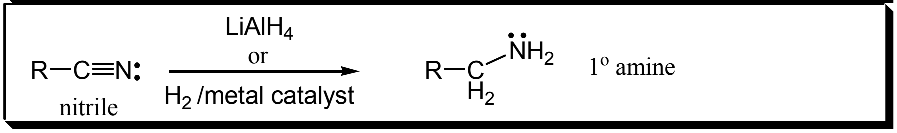
27.2



27.3



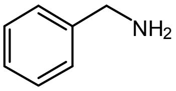
27.4



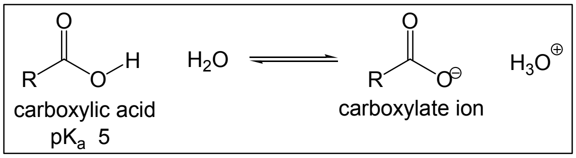
Critical Thinking Questions

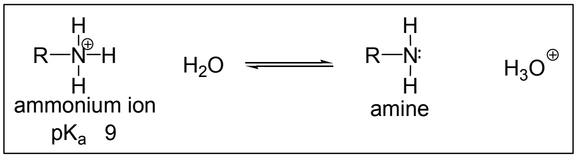
9. What do Synthetic Transformations 27.1-27.3 accomplish that the reactions in Model 2 do not?

10. Show at least one way of making benzyl amine (below) using ammonia (NH_3) as your original nitrogen source. (There are several possible ways, which is the subject of an Exercise question.)

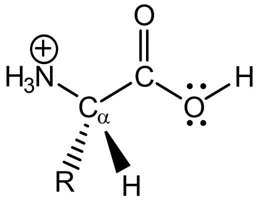


11. A conjugate acid-base pair is shown in each box below. For each box, circle the form (conjugate acid or base) you expect to be more abundant in a solution buffered to pH 7 (biological pH).





Model 4: Amino Carboxylic Acids (amino acids)



Twenty common **amino acids** are found in biological systems. Each differs from the others in the identity of the R group. **Proteins** are **polymers** (long chains) of these 20 amino acids. By convention, amino acids (or chains of amino acids called **peptides** or **proteins**) are drawn with the amine end to the left and the carboxylic acid end to the right.

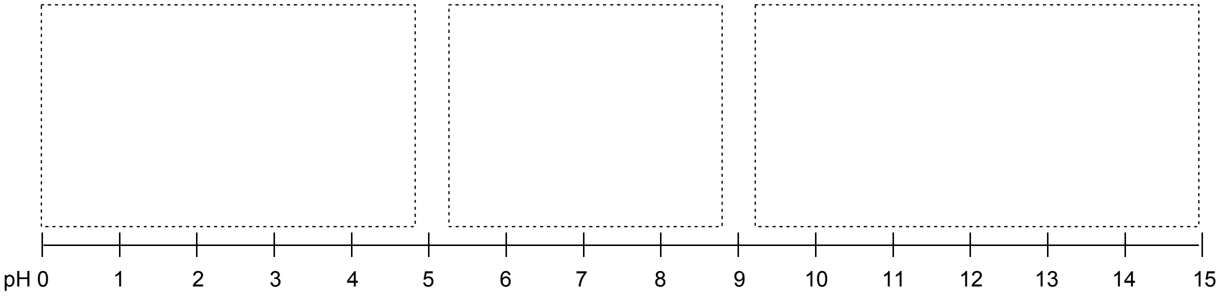
Critical Thinking Questions

12. Water solutions are limited to a pH range of about 0-15. Based on the information in Model 4…

    a. Over what pH range will the form of the amino acid shown in Model 4 dominate?

    b. Draw the dominant form of an amino acid at pH 7. Assume that the amino and carboxy ends of an amino acid have the same pK_a values as an isolated amine and an isolated carboxylic acid, respectively.

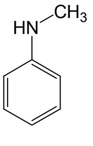
    c. (Check your work.) In each box on the graph below, draw the form of an amino acid that is expected to dominate over the pH range covered by the box.

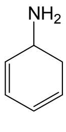


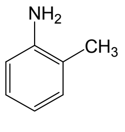
Exercises for Part A

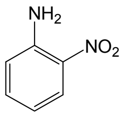
1. Draw all three second-order resonance structures of aniline, and explain why aromatic amines are weak bases and poor nucleophiles (as compared to **non-aromatic amines**).

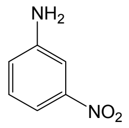
2. Indicate if each molecule is a stronger or weaker base than aniline, and explain your reasoning.

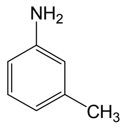


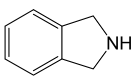


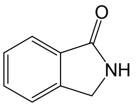










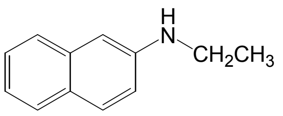


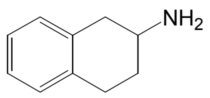
3. Do your best to order the molecules in the previous question from strongest base to weakest base.

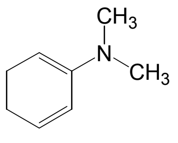
4. Use wedge-and-dash bonds to draw a 3-D representation of ammonia.
   a. Label your drawing with the word used to describe the shape of this molecule.
   b. What is the **hybridization state** of the N in ammonia?

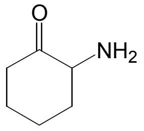
5. Ordinary amines cannot be chiral. This is because the lone pair does not hold a fixed position around the N like a bonding pair of electrons. The lone pair of an amine is constantly "flipping" back and forth, changing the configuration of amine.
   a. However, ammonium salts can be chiral. Draw a wedge-and-dash representation of the **R** enantiomer of the conjugate acid of *N*-ethyl-*N*-methylpropylamine.
   b. Consider the following reaction: If a sample of the pure **R** ammonium salt you drew above is treated with base and then acid, will the resulting sample be **pure R**, **pure S**, or **a racemic mixture**? (Circle one and explain your reasoning.)

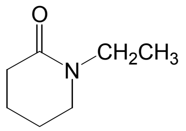
6. Place the following labels on the molecules below. Some will have more than one label, some will have no labels. **Aromatic Molecule; Aromatic Amine; Amide**

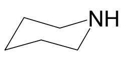


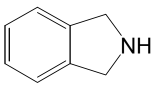


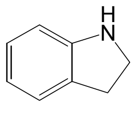






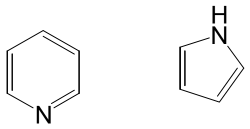






7. Indicate the approximate p*Ka* of the conjugate acid of each compound above by writing one of… **pK_a about 0; pK_a about 5; pK_a about 10.**

8. Which of the following aromatic compounds is more basic? Explain your reasoning.

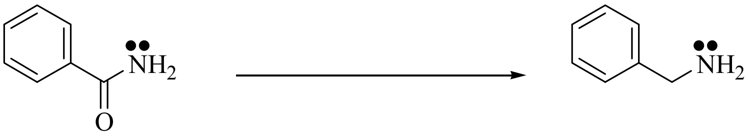


9. Show three different ways of making benzyl amine (see CTQ 10) using ammonia (NH_3) as your original nitrogen source.

10. In what pH range (if any) is an amino acid likely to...
    a. have no positive or negative formal charges on any of its atoms?
    b. be overall neutral?

11. Show the mechanisms of each step in a Gabriel synthesis (See Model 3.).

12. Consider the reaction below.



    a. Write appropriate reagents over the reaction arrow.
    b. As a result of this reaction, is the N made more nucleophilic or less nucleophilic?
    c. Draw second-order resonance structures to support your answer in part b.

13. Biologists often refer to one of the carbons in an amino acid as the alpha carbon. Identify the alpha carbon on the amino acid in Model 4, and devise an explanation for this terminology.

14. Biological amino acids are called L-amino acids. By convention this terminology means that they appear as the amino acid shown in Model 4 (with the H coming out of the page and the R group going into the page when the amino terminus is to the left). However, not all L-amino acids have the same absolute configuration (R vs. S). What is the absolute configuration (R or S) of an amino acid with…

R = CH_3? R = isopropyl? R = CH_2OH? R = $CH_2C_6H_5$? R = CH_2SH

15. (Check your work.) All of the amino acids above have the same absolute configuration EXCEPT the last one. It turns out that 19 of the 20 naturally occurring L-amino acids have the same absolute configuration. Only cysteine (R = CH_2SH) is different. Explain why cysteine has a different absolute configuration even though, like the others, it has an H coming out of the page and the R group going into the page (with the amino terminus on the left).

16. Read the assigned pages in your text, and do the assigned problems.

The Big Picture

Amines are typically the last of the non-biochemical organic chemistry topics. This is because they are a jumping off point for understanding some of the most important biological molecules and their biochemistry. Model 4 begins this exploration with the introduction of amino acids, the building blocks of proteins.

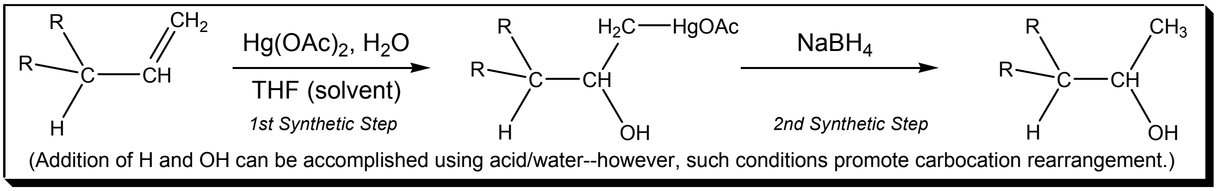
A deep understanding of **biochemistry** requires a deep and mechanistic understanding of organic chemistry. Many students using this book will now go on to study other types of biomolecules. The main ones are sugars (a.k.a. carbohydrates), fats (a.k.a. lipids), and nucleic acids (e.g. DNA, RNA). Those of you who decide to use your foundation in organic chemistry to go onto a biochemistry course will be rewarded for your hard work in this course. Many students who end up in the biological or health sciences say that the reason to learn organic chemistry is to understand the fascination and dynamic world of biochemistry.

Common Points of Confusion

- pK_a is a central topic in organic chemistry. If you are not comfortable with this topic yet, now is a chance to really hone your understanding. One common point of confusion regarding pK_a's and amines is that the pK_a often associated with an amine is actually the pK_a of the amine's conjugate acid. The only exception to this is if you are talking about taking an H off of a neutral amine. The pK_a associated with this process is 35, indicating that it is very very difficult to remove such an H. For a review of pK_a see CA 4.
- An amine that is not attached directly to an aromatic ring is called an **aliphatic amine**. The term **aromatic amine** is reserved for a molecule with an amine group attached directly to an aromatic ring. Do not confuse this with aromatic molecules that have an amine group NOT attached to the aromatic ring. Such a molecule (e.g. benzyl amine in CQT 4a) might reasonably be called an aromatic molecule with an aliphatic amine.
- Students often forget that, though amines are very good nucleophiles, it is not generally useful to directly alkylate an amine using an alkyl halide electrophile. This is because the product of this reaction (the alkylated amine) is likely a better nucleophile than the starting amine. The result is a mess of products. These difficulties gave rise to the special means of generating amines (especially primary amines) showcased in Model 3.
- Biochemical topics almost always involve stereochemistry. This is because most biological molecules are chiral, and only the correct stereoisomer has the appropriate biological activity. This issue is complicated by the fact that biochemists do not usually use the R/S nomenclature for stereocenters. Instead, the **D/L nomenclature** is used. This simplifies things in certain cases. For example, all 20 of the key amino acids are **L-amino acids**; and this matches up pretty well with the fact that 19 of 20 have an absolute configuration of S. However, since cysteine has a sulfur side chain it causes a priority ranking switch and **cysteine** ends up having an absolute configuration of R. Watch out for this and other disconnects between the D/L naming system and the R/S naming system. (For sugars, the match between the D/L and R/S naming systems is even less close, and is explained in Model 10 of CA 12.)

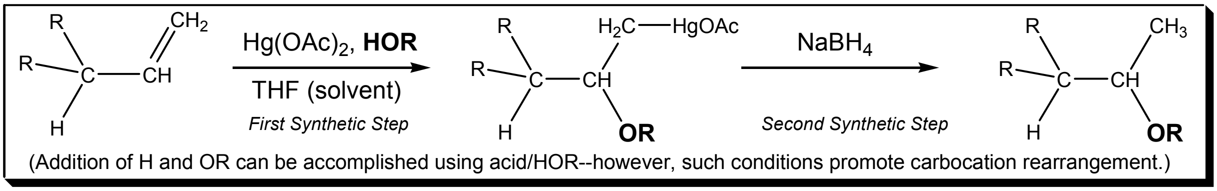
Appendix: Synthetic Transformations

Synthetic Transformation 8.1: Addition of H and OH without rearrangement (Oxymercuration-Demercuration)



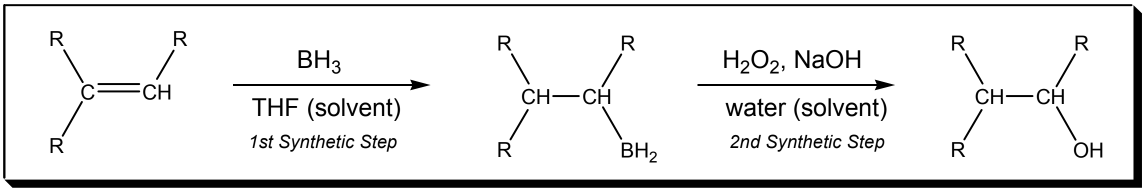
(Addition of H and OH can be accomplished using acid/water--however, such conditions promote carbocation rearrangement.)

Synthetic Transformation 8.2: Addition of H and OR without rearrangement (Alkoxymercuration-Demercuration)

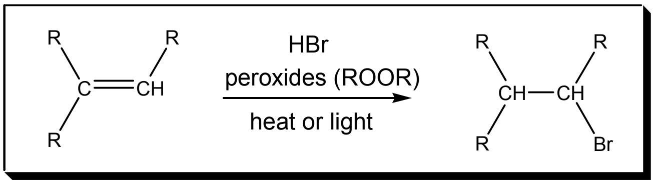


(Addition of H and OR can be accomplished using acid/HOR--however, such conditions promote carbocation rearrangement.)

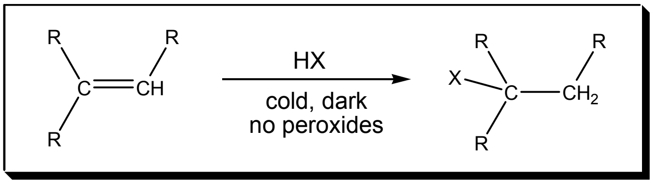
Synthetic Transformation 8.3: Anti-Markovnikov Addition of H and OH



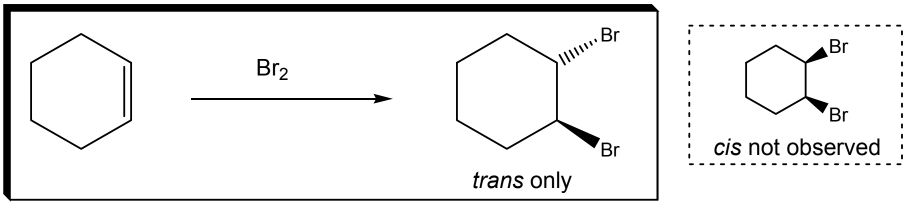
Synthetic Transformation 8.4: Anti-Markovnikov Addition of H and Br



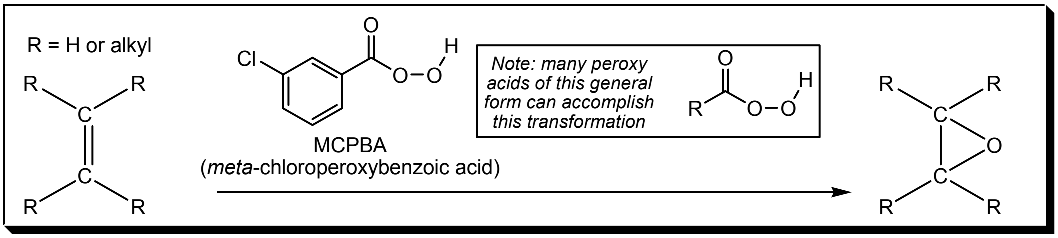
(*from Part A*) Synthetic Transformation 8.5: Markovnikov Addition of H and X (X = Cl, Br, or I)



Synthetic Transformation 9.1: Addition of Br_2 to an Alkene

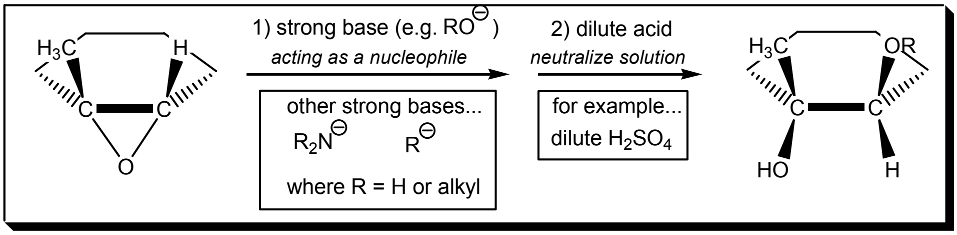


Synthetic Transformation 9.2: Oxidation of an Alkene to an Epoxide

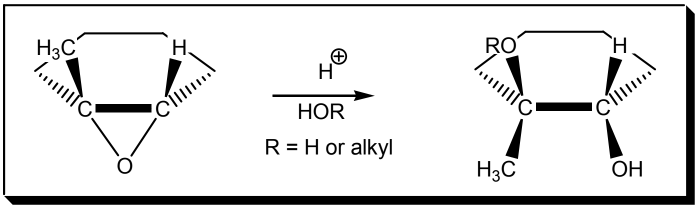


Note: many peroxy acids of this general form can accomplish this transformation

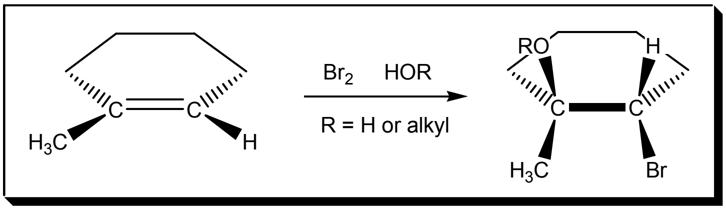
Synthetic Transformation 9.3: anti-Markovnikov Epoxide Ring Opening (Basic Conditions)



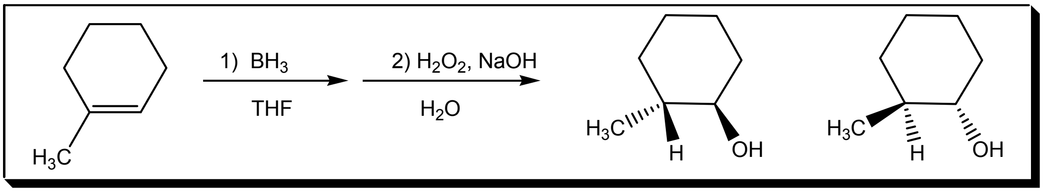
Synthetic Transformation 9.4: Markovnikov Epoxide Ring Opening (Acidic Conditions)



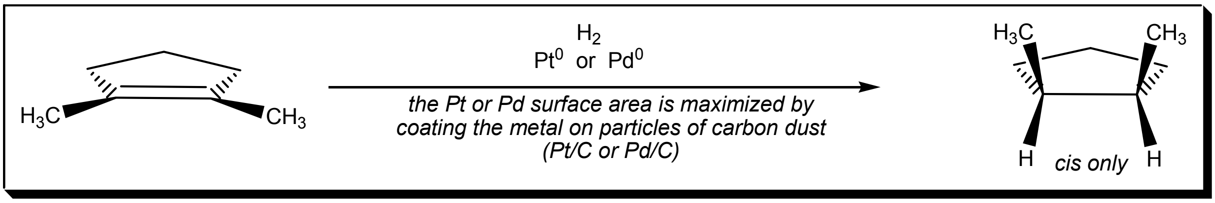
Synthetic Transformation 9.5: Markovnikov Addition of Br and OR to an Alkene



Synthetic Transformation 10.1: Hydroboration-Oxidation



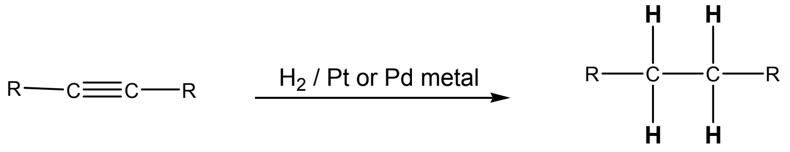
Synthetic Transformation 10.2: Catalytic Hydrogenation



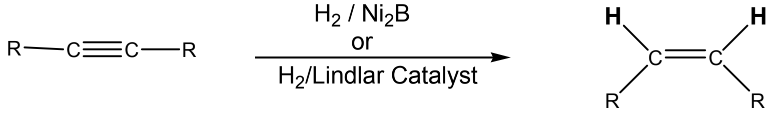
the Pt or Pd surface area is maximized by coating the metal on particles of carbon dust (Pt/C or Pd/C)

Synthetic Transformations 10.3-10.5: Stereoselective Alkyne Reductions

10.3

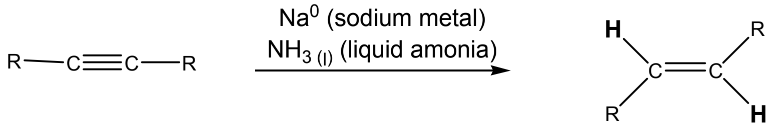


10.4



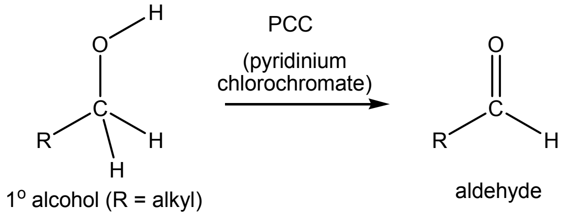
Lindlar Catalyst = Pd that has been "poisoned" (deactivated) by mixing with $CaCO_3$, quinoline and lead acetate

10.5

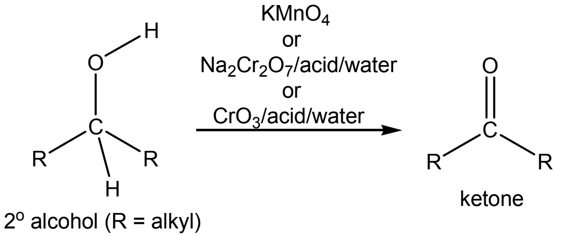


Na/NH_3 is commonly confused with the strong base $NaNH_2$ (in which Na^+ is acting as a spectator counterion)

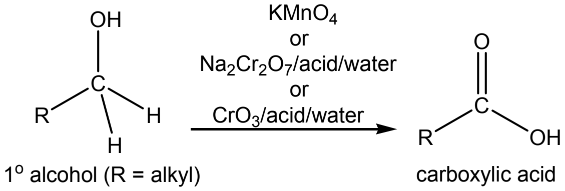
Synth Transf 10.6: Oxidation of 1° Alcohol to an Aldehyde



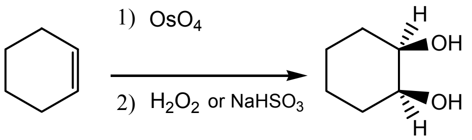
Synth Transf 10.7: Oxidation of 2° Alcohol to a Ketone



Synth Transf 10.8: Oxidation of 1° Alcohol to a CA

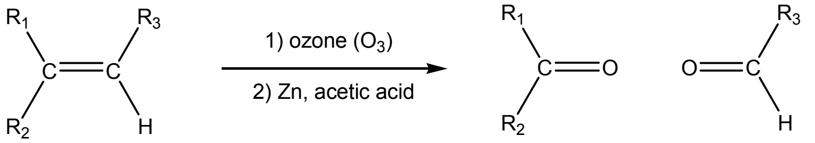


Synth Transf 10.9: Syn Addition of 2 OH Groups

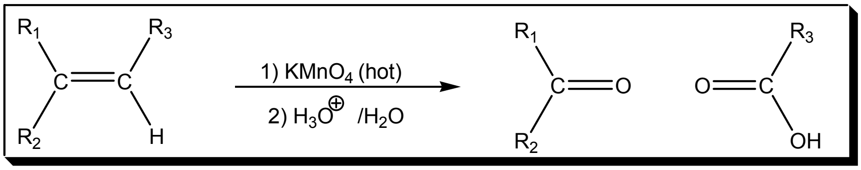


a cold, dilute $KMnO_4$ solution, followed by $KOH_{(aq)}$, can be used in place of the highly toxic OsO_4

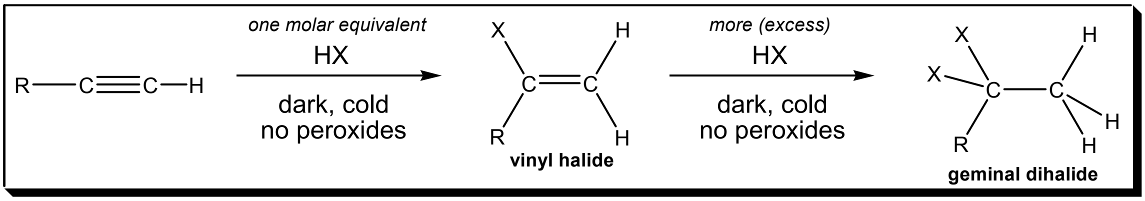
Synthetic Transformation 10.10: Cleavage of a C=C Double Bond using Ozone (Ozonalysis)



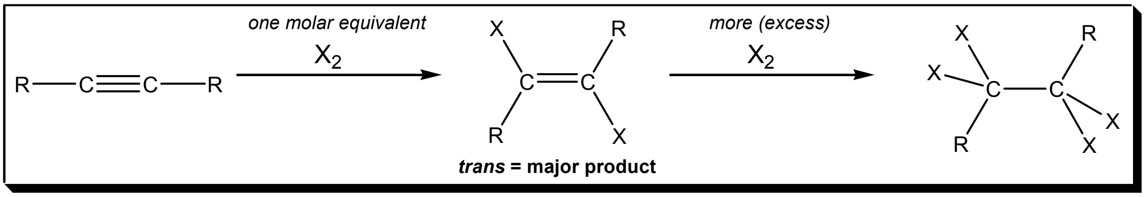
Synthetic Transformation 10.11: Cleavage of a C=C Double Bond using Permanganate (MnO_4^-)



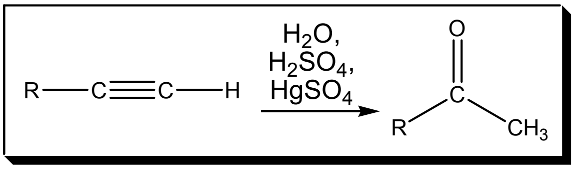
Synthetic Transformation 11.1: Markovnikov Addition of H and X (X = Cl, Br, or I)



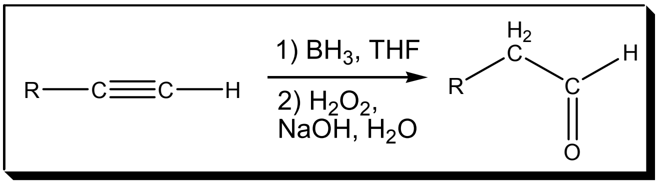
Synthetic Transformation 11.2: Addition of X_2 (X = Cl or Br)



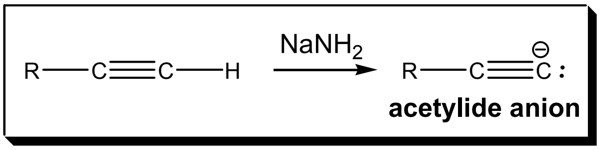
Synth Transf 11.3: Markov. Addition of H_2O to an Alkyne



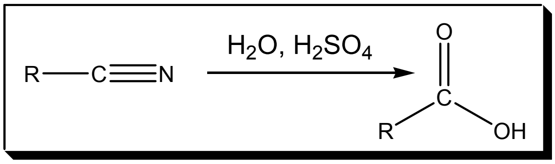
Synth Transf 11.4: anti-Markov. Add'n of H_2O to Alkyne



Synth Transf 11.5: Deprotonation of an Alkyne

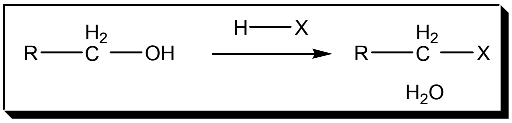


Synth Transf 11.6: Hydrolysis of a Nitrile



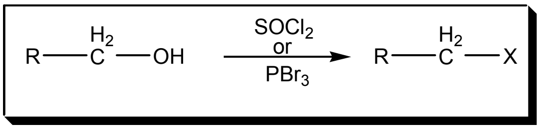
Synthetic Transformations 13.1-3: Halogenation of an Alcohol

13.1



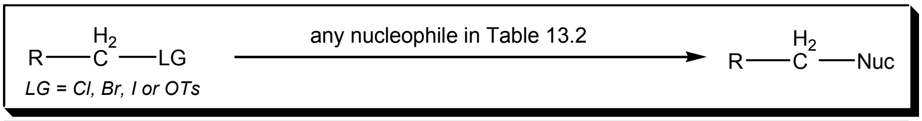
13.2

13.3

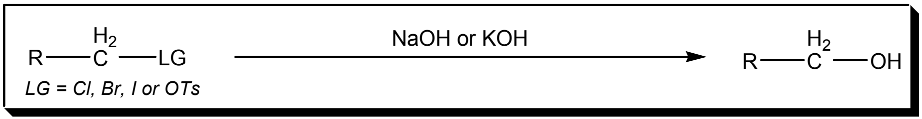


Synthetic Transformations 13.4a-d: Examples of Synthetic Uses of S_N2 Reactions

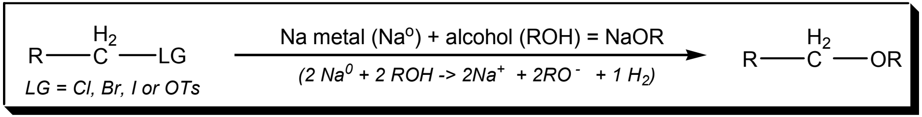
13.4a



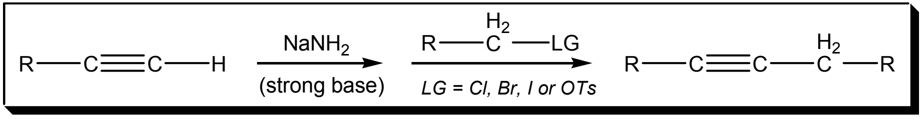
13.4b



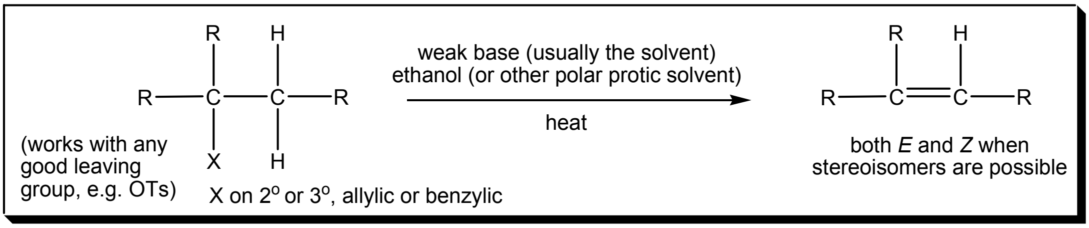
13.4c


R—CH2—LG
LG = Cl, Br, I or OTs
Na metal (Na°) + alcohol (ROH) = NaOR
(2 Na0 + 2 ROH -> 2Na+ + 2RO- + 1 H2)
R—CH2—OR

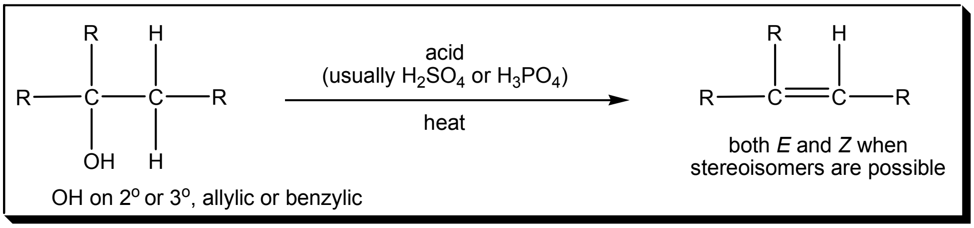
13.4d



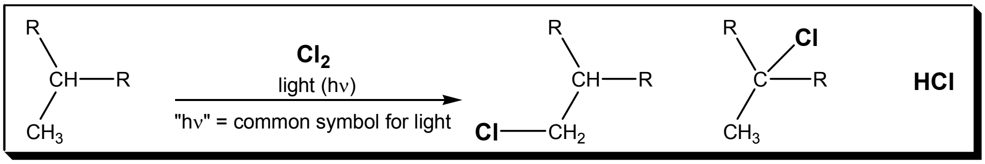
Synthetic Transformation 14.1: Alkyl Halide (R—X) or Tosylate (R—OTs) to Alkene (via E1)


R
H
R—C—C—R
X
H
(works with any good leaving group, e.g. OTs)
X on 2° or 3°, allylic or benzylic
weak base (usually the solvent)
ethanol (or other polar protic solvent)
heat
R
H
R—C=C—R
both E and Z when stereoisomers are possible

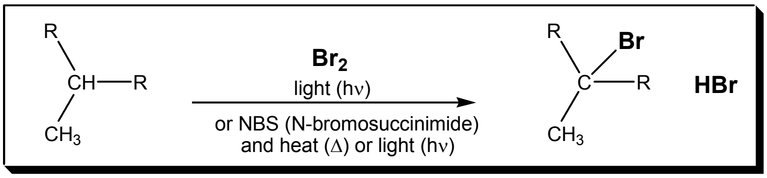
Synthetic Transformation 14.2: 2° or 3°, Allylic or Benzylic Alcohol to Alkene (via E1)

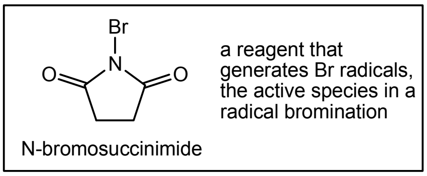

R
H
R—C—C—R
OH
H
OH on 2° or 3°, allylic or benzylic
acid
(usually H2SO4 or H3PO4)
heat
R
H
R—C=C—R
both E and Z when stereoisomers are possible

Synthetic Transformation 15.1: Radical Clorination of an Alkane

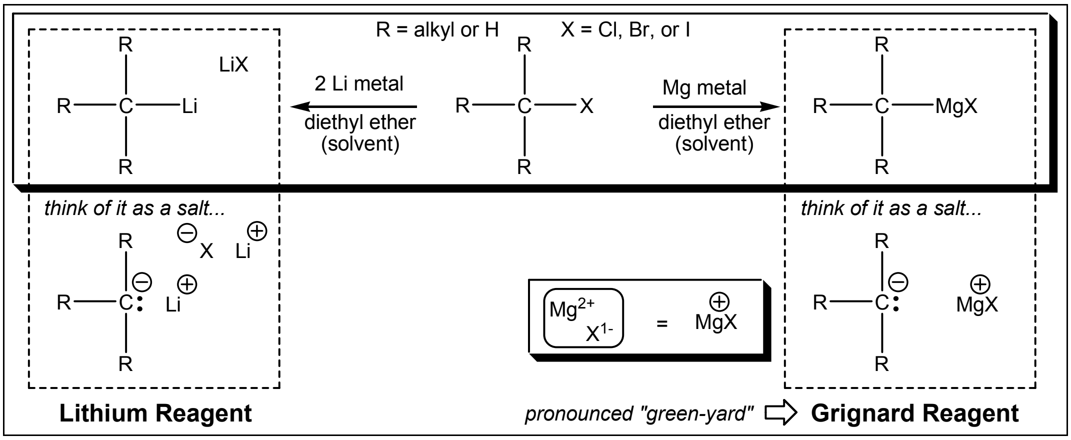


Synthetic Transformation 15.2: Radical Bromination of an Alkane

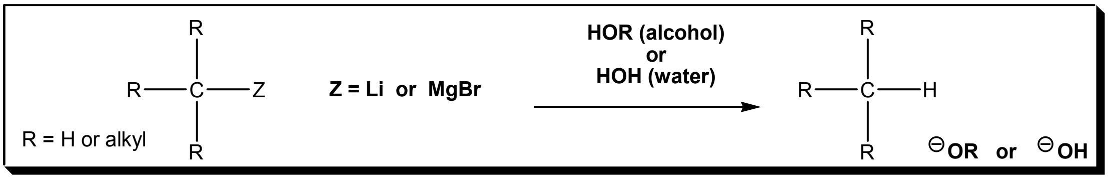



Br
N
O
O
N-bromosuccinimide
a reagent that generates Br radicals, the active species in a radical bromination

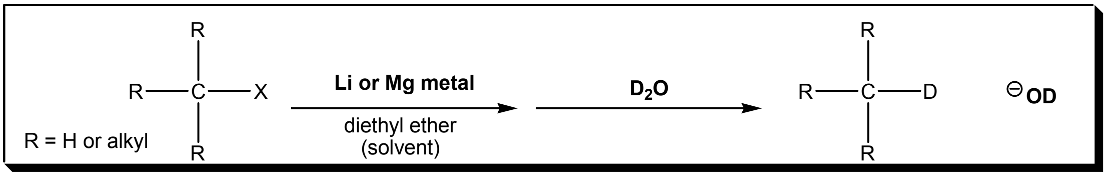
Synthetic Transformation 16.1: Lithium or Grignard Reagent from an Alkyl Halide



Synthetic Transformation 16.2: Reaction of a Lithium or Grignard Reagent as a Base

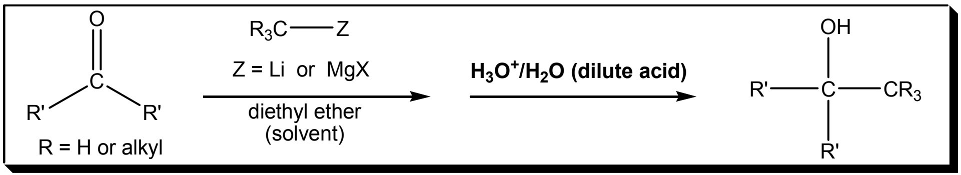

R = H or alkyl
Z = Li or MgBr
HOR (alcohol) or HOH (water)
$^{\ominus}$OR or $^{\ominus}$OH

Synthetic Transformation 16.3: Replacement of a Halogen with a Deuterium

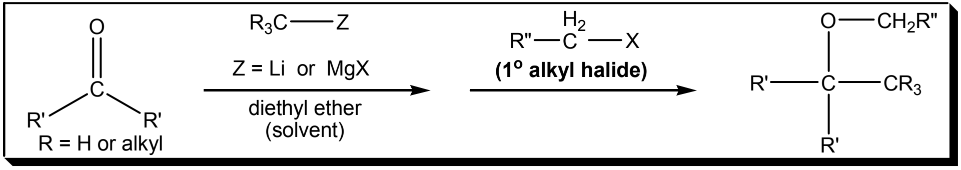


Synthetic Transformations 16.4 and 16.5: Alcohol or Ether from an Aldehyde or Ketone

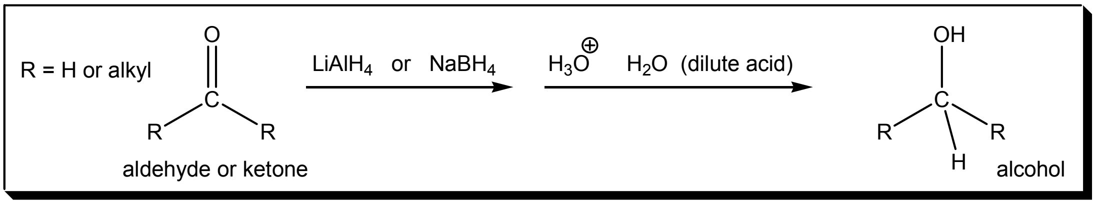
16.4



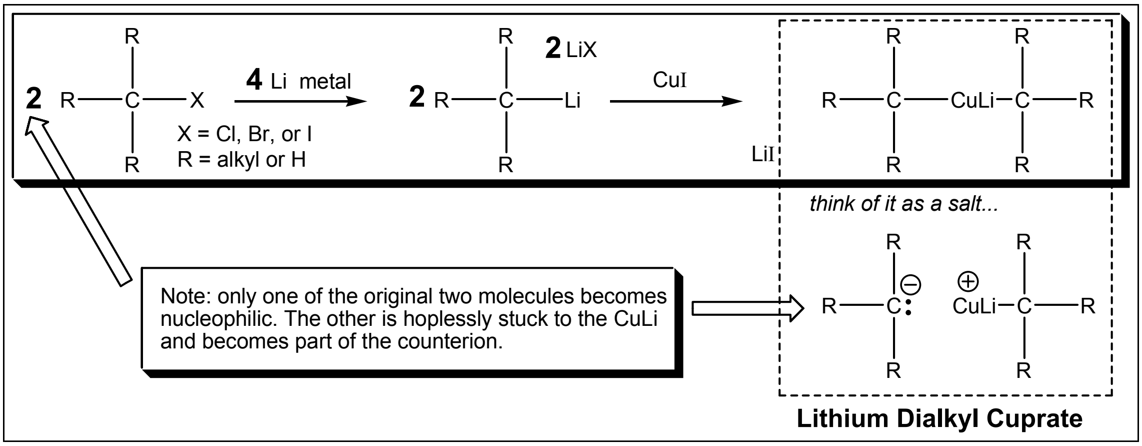
16.5



Synthetic Transformation 16.6: Reduction of an Aldehyde or Ketone to an Alcohol



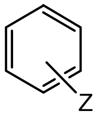
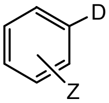
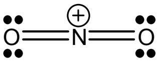
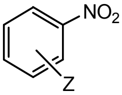
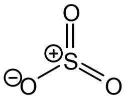
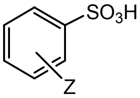
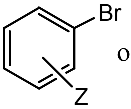
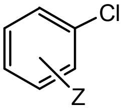
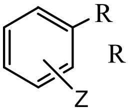
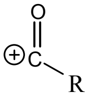
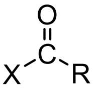
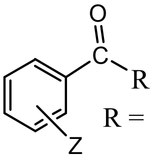
Synthetic Transformation 16.7: Lithium Dialkyl Cuprate Reagent from an Alkyl Halide


2
4 Li metal
X = Cl, Br, or I
R = alkyl or H
2
2 LiX
CuI
LiI
think of it as a salt...
Note: only one of the original two molecules becomes nucleophilic. The other is hoplessly stuck to the CuLi and becomes part of the counterion.
Lithium Dialkyl Cuprate

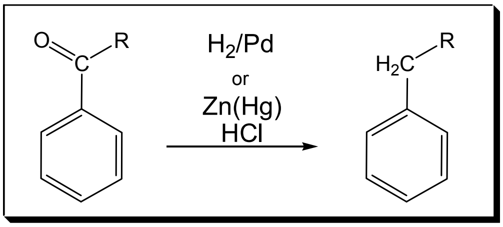
Synthetic Transformation 16.8: Reduction of a Nitro Group to an Amine

$$\mathrm{R{-}NO_2} \xrightarrow{\substack{\text{zinc metal/mercury metal amalgum = "Zn(Hg)"} \\ \mathrm{HCl}}} \mathrm{R{-}NH_2}$$

Synthetic Transformations 19.1-19.6: Reagents for EAS

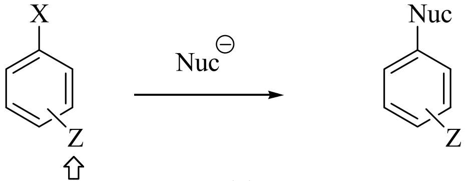
Reactant	Synth. Transf.	Electrophile (E^+)	Reagents	Product(s)
 benzene when Z = H	19.1	D^+	Any deuterated strong acid	
	19.2		H_2SO_4 and HNO_3	
	19.3		anhydrous sulfuric acid (H_2SO_4 with no water)	
	19.4	Br^+ or Cl^+	Br_2 and $FeBr_3$ or Cl_2 and $FeCl_3$	 or 
	19.5	R^+	R-X, AlX_3 (X = Cl or Br)	 R = alkyl group
	19.6		 AlX_3 (X = Cl or Br)	 R = alkyl group

Synthetic Transformation 19.7: Reduction of a Benzyl Carbonyl



Note that Zn(Hg)/HCl has no effect on ordinary C=C π bonds.

Synthetic Transformation 21.1: NAS (Nucelophilic Aromatic Substitution)



X = F, Cl, Br or I

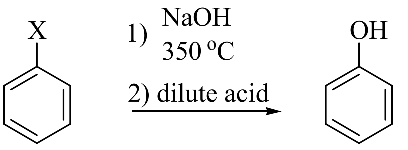
Z = Strong EWG, e.g. NO_2, carbonyl, or $\overset{\oplus}{N}R_3$

Nuc = $^{\ominus}OH$ $^{\ominus}OR$ or R_3N

under normal condition there must be at least one EWG *ortho* or *para* to leaving group (Certain conditions do not require an EWG. See Synth. Transf's 21.2 & 21.3 in Exercises)

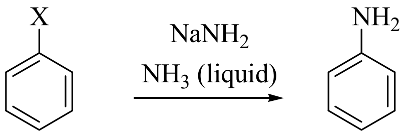
Synthetic Transformations 21.2 and 21.3: Benzyne Reactions

21.2



X = Cl, Br or I

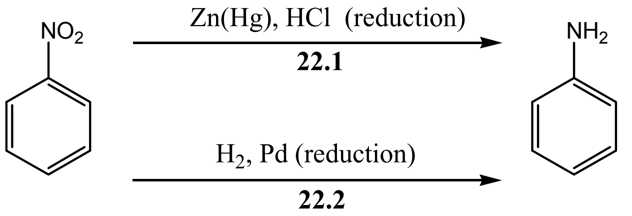
21.3



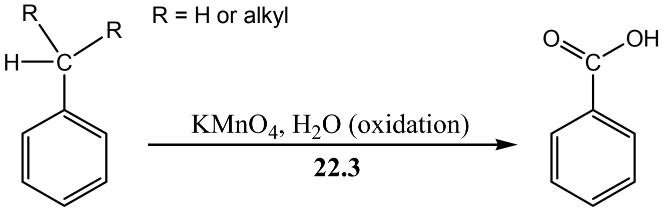
X = Cl, Br or I

Synthetic Transformations 22.1-22.3: Changing an *o/p* to a *m* Director, or Vice Versa

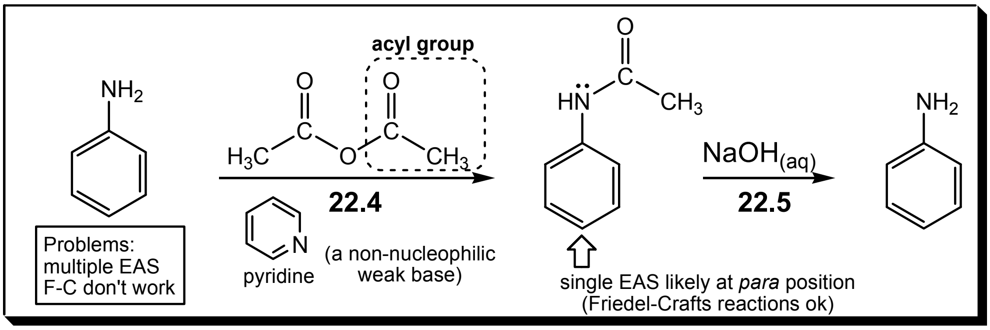
Synthetic Transformations 22.1-22.2



Synthetic Transformation 22.3

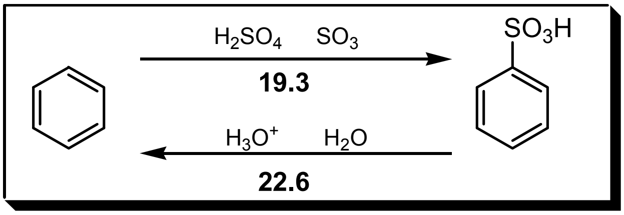


Synthetic Transformations 22.4 and 22.5: Acylation and de-Acylation of Anilines

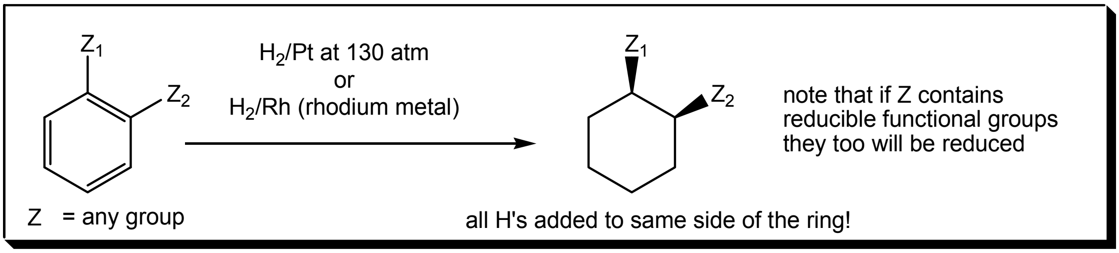

NH2
acyl group
O
O
H3C
C
O
C
CH3
22.4
N
pyridine
(a non-nucleophilic weak base)
Problems:
multiple EAS
F-C don't work
O
C
HN
CH3
single EAS likely at *para* position
(Friedel-Crafts reactions ok)
NaOH(aq)
22.5
NH2

The mechanisms of both these reactions will be covered in the next ChemActivity.

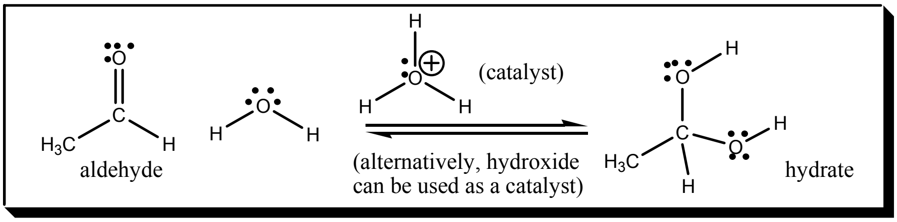
Synthetic Transformations 22.6 (and 19.3): Sulfonation and de-Sulfonation of Aromatic Rings



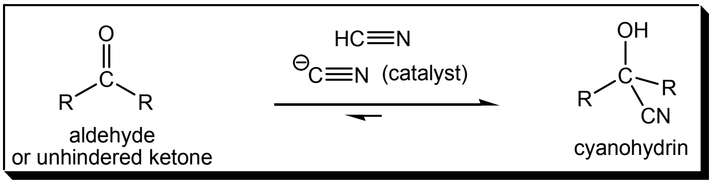
Synthetic Transformation 22.7: Complete Reduction of Benzene


Z1
Z2
Z = any group
H2/Pt at 130 atm
or
H2/Rh (rhodium metal)
Z1
Z2
note that if Z contains reducible functional groups they too will be reduced
all H's added to same side of the ring!

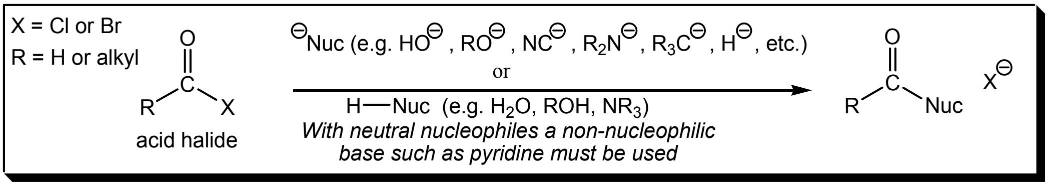
Synthetic Transformation 23.1: Hydrate Formation



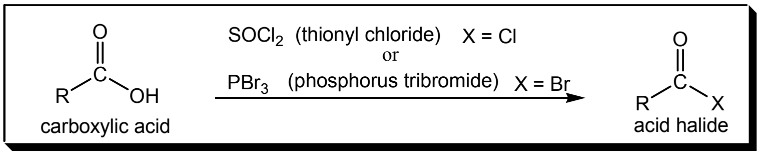
Synthetic Transformation 23.2: Cyanohydrin Formation



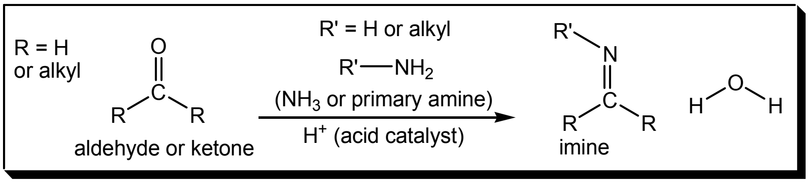
Synthetic Transformation 23.3: Acid Halide Reaction (Nucleophilic Acyl Substitution)


X = Cl or Br
R = H or alkyl
acid halide
$^{\ominus}$Nuc (e.g. $HO^{\ominus}$, $RO^{\ominus}$, $NC^{\ominus}$, $R_2N^{\ominus}$, $R_3C^{\ominus}$, $H^{\ominus}$, etc.)
or
H—Nuc (e.g. H_2O, ROH, NR_3)
With neutral nucleophiles a non-nucleophilic base such as pyridine must be used
Nuc
$X^{\ominus}$

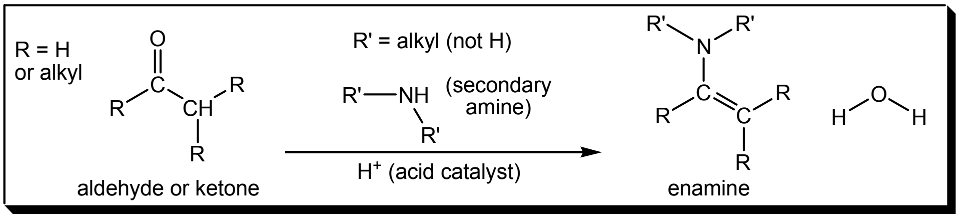
Synthetic Transformation 23.4: Preparation of Acid Halides from Carboxylic Acids


carboxylic acid
$SOCl_2$ (thionyl chloride) X = Cl
or
PBr_3 (phosphorus tribromide) X = Br
acid halide

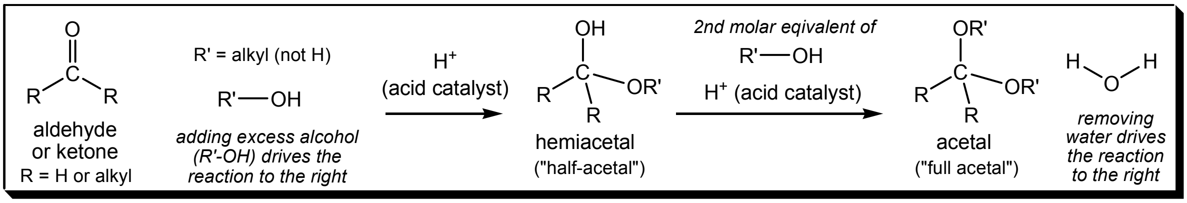
Synthetic Transformation 23.5: Imine Formation



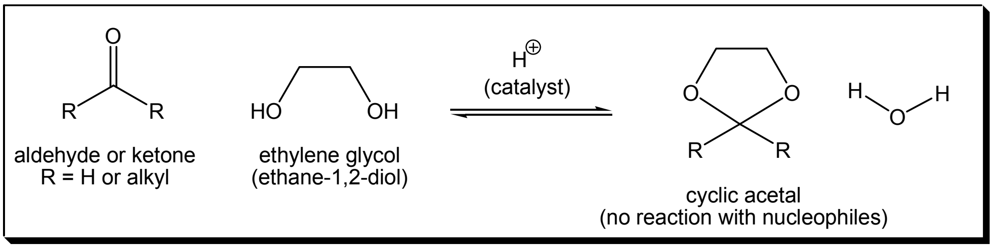
Synthetic Transformation 23.6: Enamine Formation



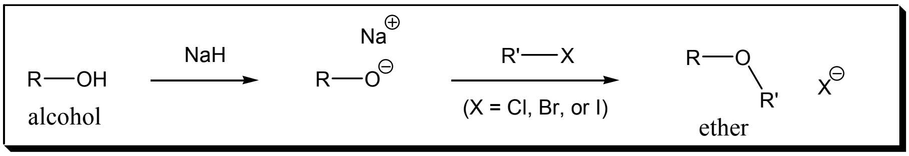
Synthetic Transformation 23.7: Hemiacetal and Acetal Formation



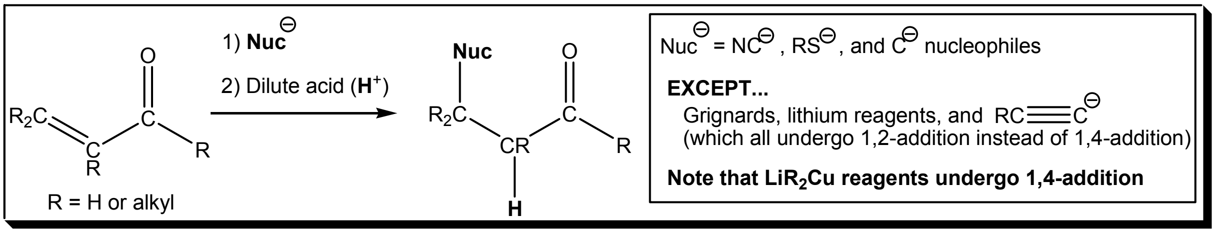
Synthetic Transformation 23.8: Protection of a Carbonyl Against Nucleophiles



Synthetic Transformation 23.9: Williamson Ether Synthesis



Synthetic Transformation 23.10: 1,4-Addition to an α,β-Unsaturated Carbonyl



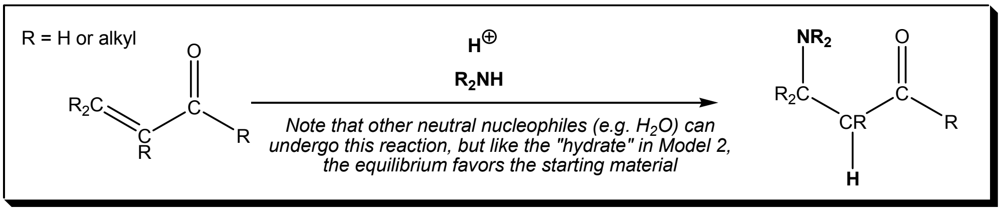
Nuc⊖ = NC⊖, RS⊖, and C⊖ nucleophiles

EXCEPT...

Grignards, lithium reagents, and RC≡C⊖ (which all undergo 1,2-addition instead of 1,4-addition)

Note that LiR_2Cu reagents undergo 1,4-addition

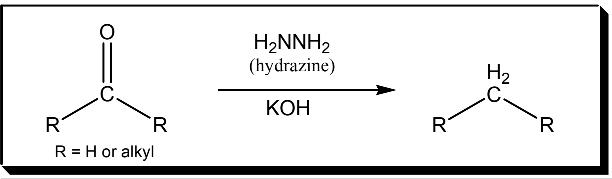
Synthetic Transformation 23.11: 1,4-Addition of an Amine to an α,β-Unsaturated Carbonyl



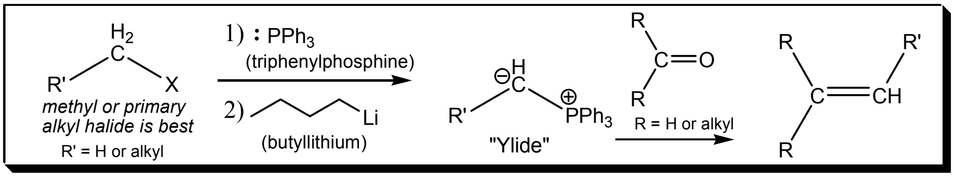
Note that other neutral nucleophiles (e.g. H_2O) can undergo this reaction, but like the "hydrate" in Model 2, the equilibrium favors the starting material

Synthetic Transformations 23.12 and 23.13: Wolff-Kishner and Wittig Reactions

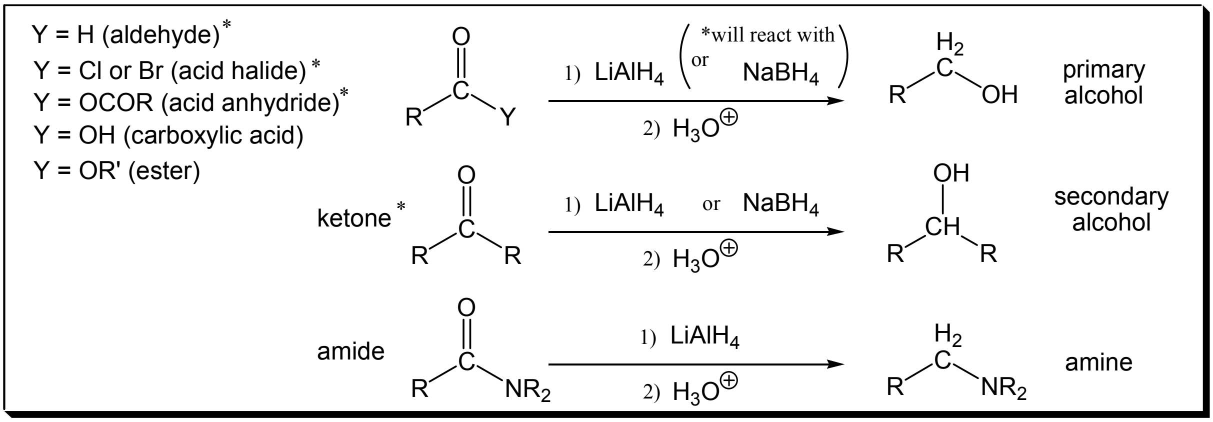
23.12 Wolff-Kishner Reaction



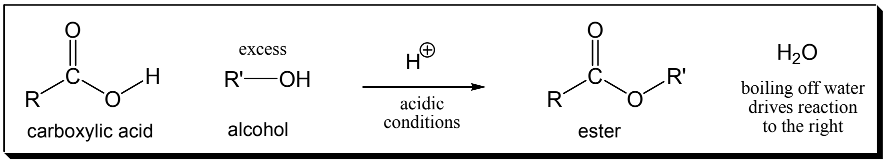
23.13 Wittig Reaction



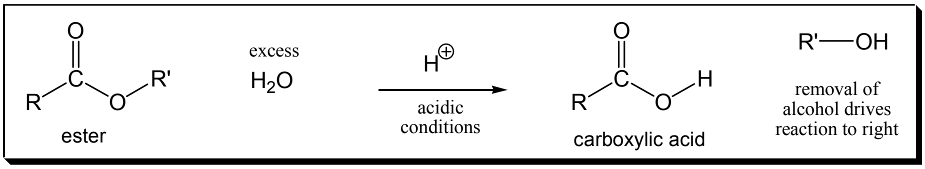
Synthetic Transformation 24.1: Reduction of Carboxylic Acid Derivatives with Hydride


Y = H (aldehyde)*
Y = Cl or Br (acid halide)*
Y = OCOR (acid anhydride)*
Y = OH (carboxylic acid)
Y = OR' (ester)

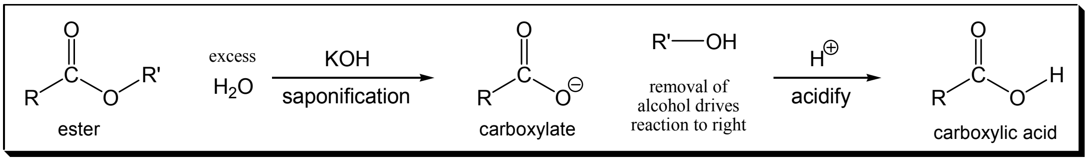
Synthetic Transformation 24.2: Acid-Catalyzed Ester Synthesis



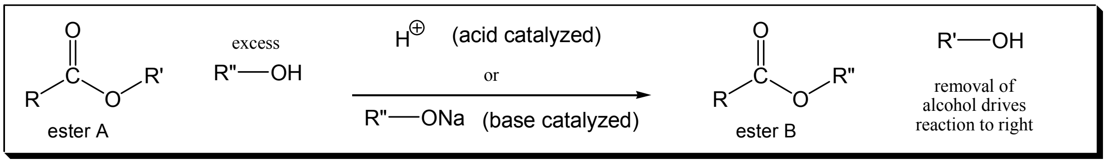
Synthetic Transformation 24.3: Acid-Catalyzed Synthesis of a CA from an Ester



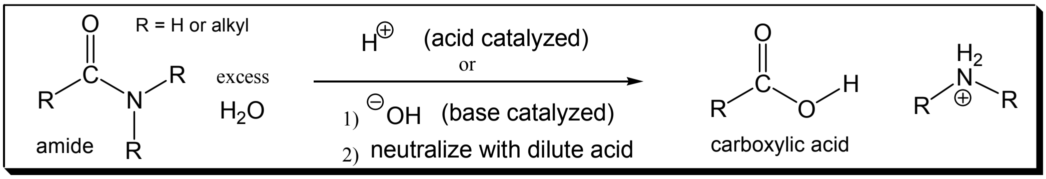
Synthetic Transformation 24.4: Ester Saponification (Base-Catalyzed CA Synthesis)



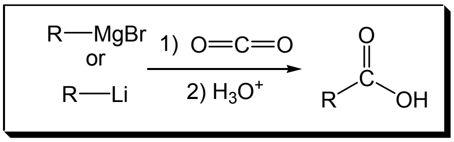
Synthetic Transformation 24.5: *Trans*-Esterification



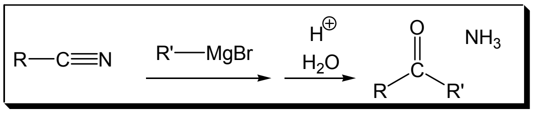
Synthetic Transformation 24.6: Acid- or Base-Catalyzed Hydrolysis of an Amide



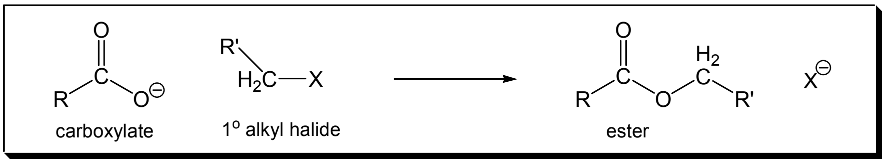
Synth. Transf. 24.7: Grignard/Lithium Rgnt + CO_2



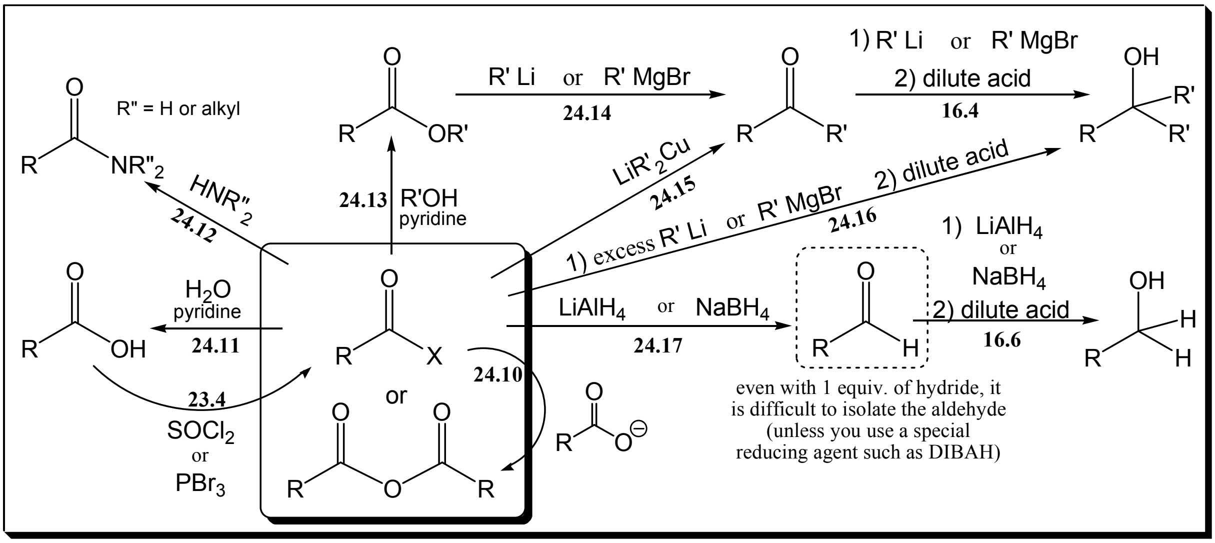
Synth. Transf. 24.8: Grignard/Lithium Rgnt + Nitrile



Synthetic Transformation 24.9: Formation of an Ester from a 1° Alkyl Halide

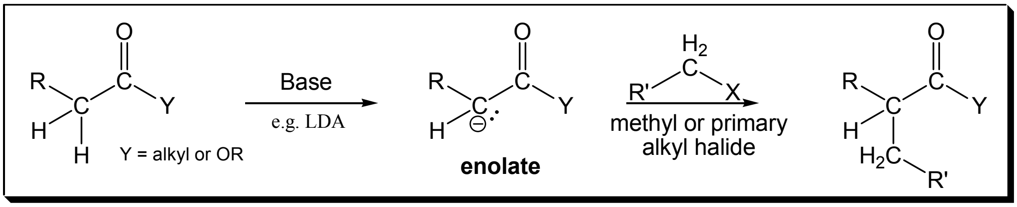


Synthetic Transformations 24.10-24.17: Reactions of Acid Halides and Anhydrides

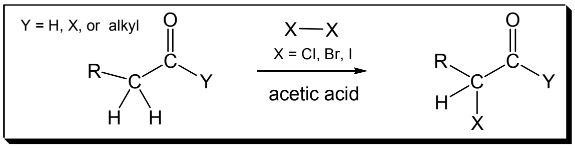


even with 1 equiv. of hydride, it is difficult to isolate the aldehyde (unless you use a special reducing agent such as DIBAH)

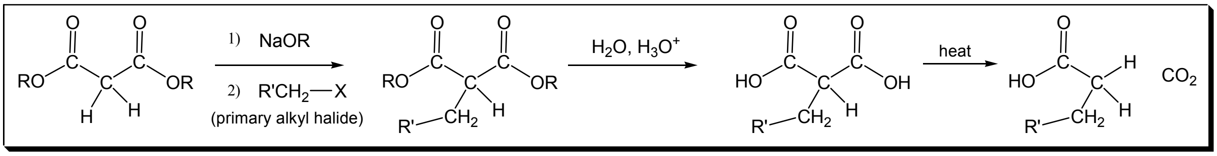
Synthetic Transformation 25.1: Base-Promoted α-Alkylation of Carbonyl Compounds



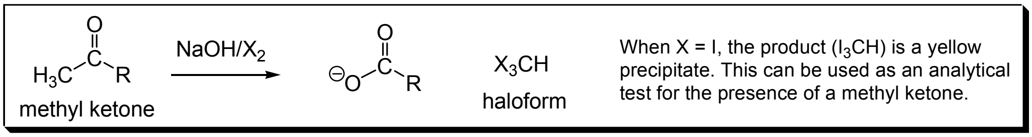
Synthetic Transformation 25.2: Acid-Catalyzed α-Halogentation of Carbonyl Compounds



Synthetic Transformation 25.3: Malonic Ester Synthesis of Carboxylic Acids

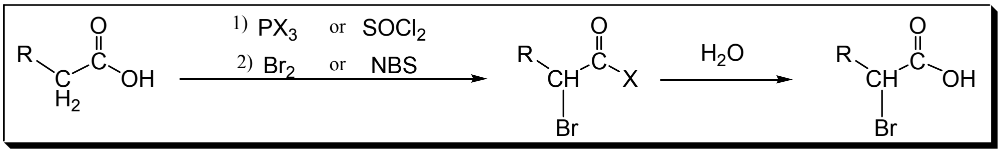


Synthetic Transformation 25.4: Haloform Reaction (and Iodoform Test for Methyl Ketones)

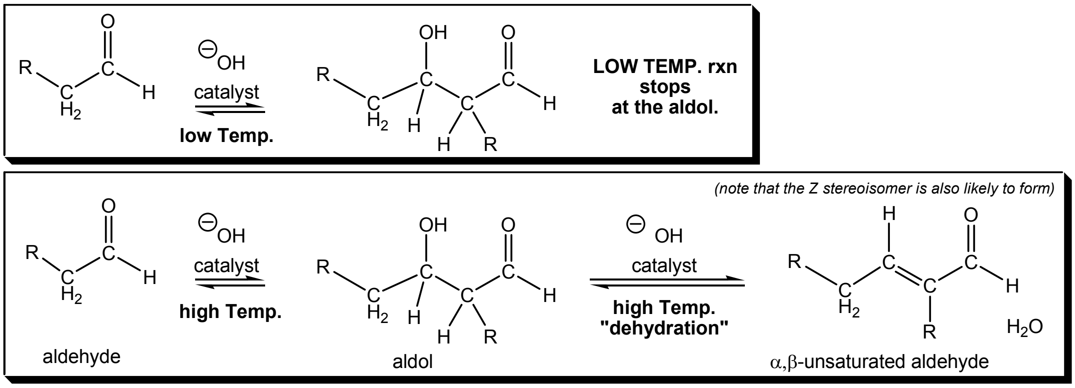


When X = I, the product (I_3CH) is a yellow precipitate. This can be used as an analytical test for the presence of a methyl ketone.

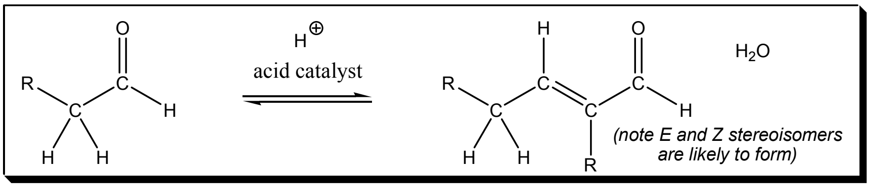
Synthetic Transformation 25.5: α-Bromination of Carboxylic Acids (Hell-Vollhard-Zelinsky)



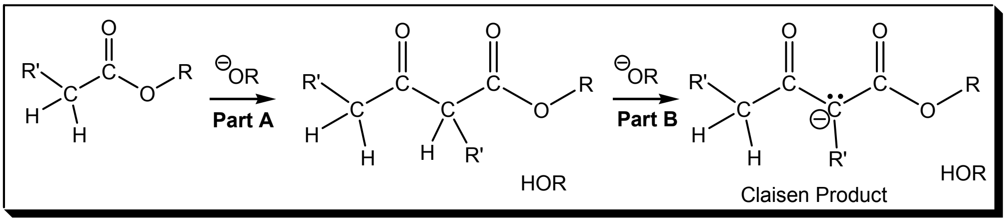
Synthetic Transformations 26.1 and 26.2: Base-Catalyzed Aldol Reactions



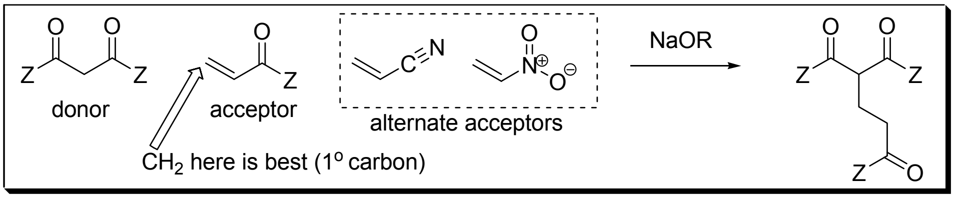
Synthetic Transformations 26.3: Acid-Catalyzed Aldol Reaction



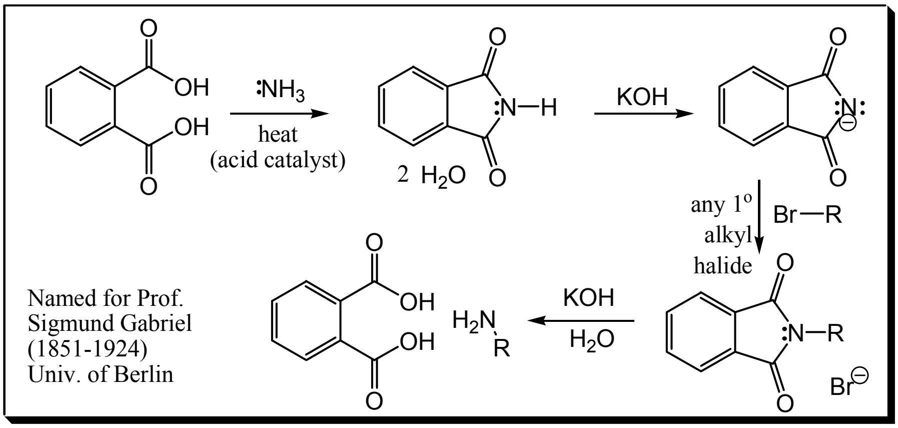
Synthetic Transformation 26.4: Claisen Reaction



Synthetic Transformation 26.5: Michael Reaction



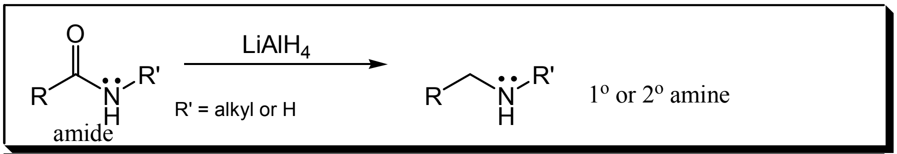
Synthetic Transformation 27.1: Gabriel Synthesis of Primary (1°) Amines



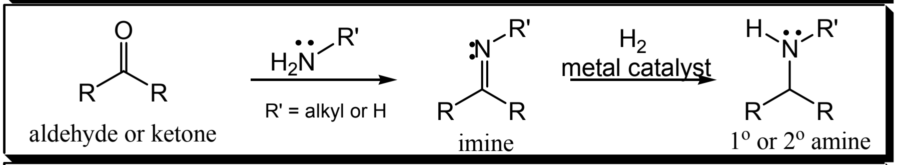
Named for Prof.
Sigmund Gabriel
(1851-1924)
Univ. of Berlin

Synthetic Transformations 27.2-27.4: Synthesis of Amines via Reduction of Amides, Aldehydes, Ketones or Nitriles

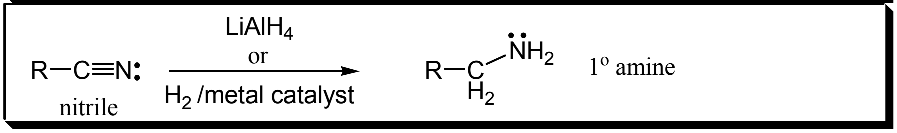
27.2



27.3



27.4



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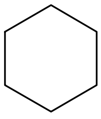
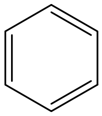


50

$H_2C{=}CH_2$

45



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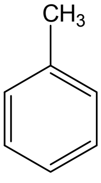

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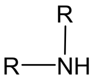
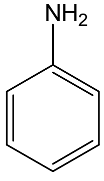


R_2NH

35



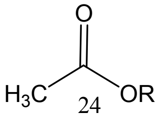
28

$H{-}H$

40

$F_3C{-}H$

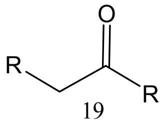
32



24

$H{-}C{\equiv}CR$

25



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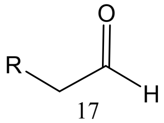

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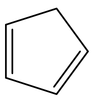


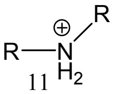
15

$R{-}OH$

16

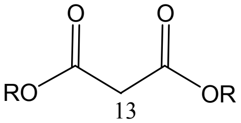
H_2O

15.7



$R_2NH_2^{\oplus}$

11



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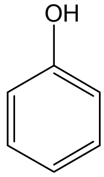

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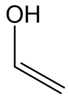
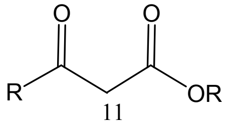


10.5

$R{-}\overset{\oplus}{N}H_3$

10.6



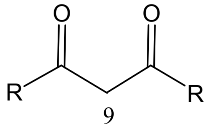
11

$H_3C{-}NO_2$

10.2

$\overset{\oplus}{N}H_4$

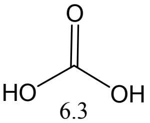
9.2



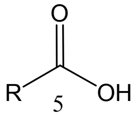
9

$H{-}CN$

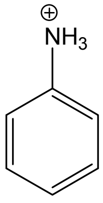
9.1



6.3



5



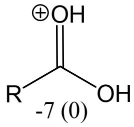
4.6

$H{-}N_3$

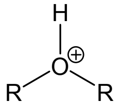
4.6

$H{-}F$

3.2



-7 (0)



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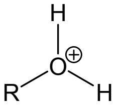
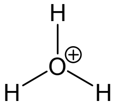
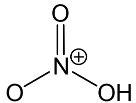


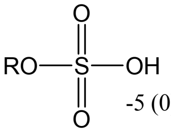
-2 (0)



-1.7 (0)



-1.4 (0)



-5 (0)

$H{-}Cl$

-2.2 (0)

$H{-}Br$

-4.7 (0)

$H{-}I$

-5.2 (0)